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**LABORATORY ANIMAL ALLERGY (LAA) AMONG
THE ANIMAL FACILITIES' WORKERS IN A
RESEARCH INSTITUTE: A CLINICAL SURVEY**



**MASTER OF SCIENCE
(OCCUPATIONAL SAFETY AND HEALTH MANAGEMENT)
UNIVERSITI UTARA MALAYSIA
AUG 2019**

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THE ANIMAL FACILITIES' WORKERS IN A
RESEARCH INSTITUTE: A CLINICAL SURVEY**

By



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**Dissertation Submitted to
Othman Yeop Abdullah Graduate School of Business,
Universiti Utara Malaysia,
In fulfillment of the requirement for the
Master of Science (Occupational Safety and Health Management)**



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ABSTRACT

Research animal facilities had been identified as a risky environment for the development of Laboratory Animal Allergy (LAA) among the exposed workers. The risk degree is in parallel with the nature of contact, intensity of exposure and individual susceptibility. Early recognition of LAA via active clinical surveillance is imperative before it progresses into occupational asthma with chronic disability. This study aimed to determine the prevalence of LAA among animal facilities' workers in Institute for Medical Research, Malaysia together with its associated exposure or environmental risk factors. This cross-sectional study recruited a total of 87 workers exposed to animal allergen and 87 control subjects. Self-administered LAA questionnaire contained details of occupational and socio-environmental history as well as lung function test (spirometry) were employed as study tools. Statistical analysis were performed using SPSS version 20, utilizing descriptive analysis, cross tabulation, independent t-test, Mann Whitney U-test and Multivariable Logistic Regression (MLR). More than half of the exposed subjects were reported at least one LAA symptoms (58.6%) and declined lung function (56.3%). Upper respiratory symptoms were the most prevalent LAA symptoms (49.4%). There was significant association between the reported symptoms and abnormal lung profile ($p < 0.05$). In term of lung function values, the mean FEV1, median FVC and mean FEV1/FVC were significantly lower among the exposed group compared to the control group ($p < 0.001$). MLR substantiated that atopic workers, smokers and those did not comply to full PPE regularly upon animal contact were more likely to develop LAA. LAA is

an acknowledged occupational hazard. Therefore knowing the existing prevalence and its risk factors to design an effective LAA prevention program consisted of exposure avoidance as well as exposure reduction which combines the engineering control, administrative control and PPE is of paramount importance.

Keywords: laboratory animal allergy, animal workers, research animal facilities, clinical survey



ABSTRAK

Fasiliti haiwan makmal bagi tujuan penyelidikan dan eksperimen adalah berisiko tinggi dan boleh menyebabkan alahan haiwan makmal (LAA) di kalangan pekerja-pekerja makmal. Tahap risiko bergantung kepada sifat pendedahan, intensiti pendedahan dan faktor kecenderungan individu. Mengesan LAA secara awal melalui pengawasan perubatan aktif adalah penting sebelum ianya menyebabkan penyakit asma dan sebarang ketidakupayaan kronik. Kajian ini bertujuan untuk menentukan kelaziman LAA di kalangan pekerja fasiliti haiwan makmal di Institut Penyelidikan Perubatan, Malaysia serta faktor risiko pendedahan pekerjaan dan persekitaran yang berkaitan. Kajian ini merekrut sejumlah 87 orang pekerja yang terdedah kepada alergen haiwan makmal dan 87 orang pekerja yang tiada pendedahan sebagai subjek kawalan. Responden dikehendaki melengkapkan borang soal selidik LAA yang merangkumi sejarah pekerjaan dan pendedahan secara terperinci, serta menjalani ujian fungsi pulmonari (spirometri). Analisa statistik dijalankan menggunakan SPSS versi 20, dengan mengaplikasikan analisa *descriptive*, *cross tabulation*, *independent t-test*, *Mann Whitney U-test* dan juga *Multivariable Logistic Regression (MLR)*. Melebihi separuh daripada subjek yang terdedah kepada alergen haiwan makmal yang melaporkan sekurang-kurangnya satu simptom LAA (58.6%) dan dikesan penurunan fungsi pulmonary. Majoriti melaporkan simptom saluran pernafasan atasan (49.4%). Perkaitan antara simptom LAA dan penurunan fungsi pulmonary adalah ketara ($p < 0.05$), manakala dari segi nilai fungsi pulmonary, min FEV1, median FVC and mean FEV1/FVC didapati rendah dan signifikan dari segi statistik di kalangan subjek

terdedah berbanding dengan subjek kawalan($p<0.001$). Analisa MLR juga mendedahkan bahawa subjek atopik, perokok dan mereka yang tidak mematuhi penggunaan alat perlindungan persendirian (PPE) yang lengkap sewaktu kontak dengan haiwan makmal, adalah lebih cenderung untuk LAA. LAA diperakui sebagai hazard pekerjaan yang major. Justeru itu, pengetahuan mengenai prevelens sedia ada bersama dengan faktor risiko yang berkaitan adalah penting untuk perekaan program pencegahan LAA yang efektif. Program yang komprehensif perlu merangkumi pengelakan pendedahan atau pengurangan tahap pendedahan menerusi kawalan kejuruteraan, kawalan pentadbiran dan penggunaan PPE yang sesuai.

Kata kunci: alahan, haiwan makmal, pengendali haiwan, fasiliti haiwan, survei klinikal



ACKNOWLEDGEMENT

I sincerely appreciate all individuals who had become a part of present study , directly or indirectly.

First of all, I would like to express my gratitude to my Supervisor, Prof Madya Dr Fadzli Shah bin Abdul Aziz for his support and guidance throughout the study. His commitment, motivation and wisdom encouraged me to complete this study on time.

Secondly i am deeply thankful to the management of Institute for Medical Research (IMR), Kuala Lumpur under Ministry of Health for the consent for data collection. Moreover, thousand thanks to all subjects who voluntarily participated in present study and gave their full cooperation throughout the study protocol.

Lastly, I owe a special debt of gratitude to my beloved husband, parents, siblings, course mates and friends who non-stop had supported me morally and psychologically along MSc. program until the accomplishment of my research project.

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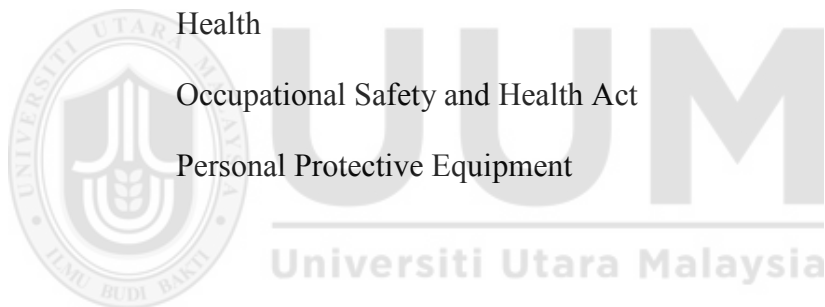
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LIST OF ABBREVIATION

DOSH	Department of Occupational Safety and Health
FEV1	Forced Expiratory Volume at one second
FVC	Forced Vital Capacity
FEV1/ FVC	The ratio of Forced Expiratory Volume at one second to Forced Vital capacity
LAA	Laboratory Animal Allergy
MLR	Multivariable Logistic Regression
NIOSH	National Institute of Occupational Safety and Health
OSHA	Occupational Safety and Health Act
PPE	Personal Protective Equipment





CHAPTER ONE

INTRODUCTION

1.1 Background of Study

The first ever occupational illness induced by laboratory animal was reported in early 1950's when a case of allergic rhinitis was addressed secondary to occupational exposure to mice (Sorrell, & Gottesman, 1957). The rodents including mice and rat are the most widely used species in medical laboratory research worldwide (Bush, Wood, & Eggleston, 1998). The laboratory animals constantly shed allergens in their body secretions and these allergens are deposited in the air or laboratory materials which make the animal facilities a high risk environment for the development of Laboratory Animal Allergy (LAA) (Jones, 2015).

Knowing the overall prevalence or incidence of Laboratory Animal Allergy (LAA) among the animal handlers is of paramount importance especially for the considerations to design the comprehensive occupational health program in order to reduce the LAA rate. Prevalence gives a measurement on the total number of LAA cases among a specific population at a particular time. Ample of studies had reported the prevalence of 11-44% in the LAA incidence across various populations (Seward, 2001). The average prevalence of 20.9% was revealed in a meta-analysis examining 19 studies (Hunnskaar, & Fosse, 1990). On the other hand, the prevalence of 23.1% revealed in a huge cross-sectional study involving a total of 5641 laboratory animal

workers in Japan (Aoyama et al., 1992). Altogether, approximately one fifth of the exposed population was estimated at risk of developing LAA upon occupational exposure.

LAA consisted of a spectrum of allergic symptoms involving eyes, skin, upper and lower airway, which range from mild to severe presentation. The most common clinical symptoms reported were nasal congestion, watery nose, sneezing and itchy or watery eyes (Aoyama et al., 1992; Cullinan et al., 1994). The allergic reaction may progress into occupational asthma in 20-30% of the sensitized individuals (Bush, Wood, & Eggleston, 1998). The diagnosis of LAA is supported by a complete yet comprehensive occupational history which is facilitated by a specific LAA questionnaire (Bernstein, Campo, & Baur, 1999), together with the lung function assessment utilizing spirometry in order to measure the degree of lung impairment.

Workers who are in regular contact with the furred laboratory animals commonly develop allergic reactions and sensitivity. Therefore, Laboratory Animal Allergy (LAA) represents a major occupational disease especially to the exposed population including animal caretakers, laboratory technicians, veterinarian and scientists where their work significantly requires such a risky exposure. The work tasks or activities associated with high level of animal allergens likes cage cleaning are more prone to respiratory or airway allergic reactions (Bush, Wood, & Eggleston, 1998).

The exposure to laboratory animals had been evidently and consistently ranked in the top three causes of occupational asthma in United Kingdom since 1989 (Gordon, 2001), although laboratory animal workers only comprised a tiny proportion of total work force in United Kingdom. In addition, the National Institute of Occupational Safety and Health in United States had also proactively recognized LAA as one of the major occupational hazard. The allergic diseases result from the exposure to a variety of laboratory animal documented a significant lost time from work (Bland, Levine, Wilson, Fox, & Rivera, 1986). Moreover, the UK countries have documented a remarkable financial burden following occupational asthma which generally requires long-term medical treatment (Ayres, Boyd, Cowie & Hurley, 2011; Jones, 2015).

Unfortunately there are very little data available on the incidence or prevalence of LAA in Malaysia. There was limited study being conducted by Ministry of Health probably because of the small number of work force working in research animal facilities compared to other more developed countries. With the notification system generated by the Occupational Health Division, Department of Occupational Safety and Health (DOSH) Malaysia, the data released to public on the trend of confirmed occupational skin and lung diseases in year 2016 and 2018 documented 25 cases (2016) and 22 cases (2018) of occupational skin disease; as well as 98 cases (2016) and 55 cases (2018) of occupational lung diseases respectively nationwide. These trend, however reported in general context without specifying the root causes (Table 1.1.1). In addition, following case investigation, those confirmed cases of occupational skin and lung diseases were categorized according to different sectors including

manufacturing, mining, farming, infrastructure, financial service and government service (Table 1.1.2). Based on the information and data released to public by DOSH, the general picture of occupational skin and lung illness specifically allergic or hypersensitivity reaction secondary to laboratory animal allergen is unclear, likely due to under reporting, overlooked or lack of awareness among both employer and employees working in animal facilities. Hence, present study hoped to generate and report the preliminary data on the LAA prevalence among workers in one of the biggest research animal facilities under Ministry of Health Malaysia so that further interventions to be planned in order improve the safety and health status of this specific exposed population at the same time to strengthen the overall occupational safety and health system.



Table 1.1.1

Confirmed cases of occupational poisoning and diseases in Malaysia, 2016 -2018

Occupational Poisoning and Diseases	No of confirmed cases (2016)	No of confirmed cases (2018)
Occupational Lung Disease	98	55
Occupational Skin Disease	25	22
Noise Induced Hearing Loss	2876	1775
Occupational Musculoskeletal Disorder	173	85
Occupational Poisoning	67	47
Diseases caused by Physical agent	2	1
Occupational Blood-borne diseases	39	13
Occupational Cancer	0	0
Psychosocial illness	0	0
Others	6	2
Total Number	3286	3058

Source: Occupational Health Division, DOSH Malaysia (2016-2018)

Table 1.1.2

Confirmed cases of occupational skin and lung diseases in Malaysia, 2016-2018 according to sectors

Occupational diseases	Manufac- turing		Minning		Farming		Infra- structure		Financial service		Govern- ment service	
	16'	18'	16'	18'	16'	18'	16'	18'	16'	18'	16'	18'
Lung Disease	15	4	2	1	1	0	1	1	6	8	66	30
Skin Disease	15	5	1	0	1	0	0	1	0	4	6	11

Source: Occupational Health Division, DOSH Malaysia (2016-2018)

1.2 Problem Statement

Animal facilities' workers are in regular and close contact with the furred animals. Therefore, one of the major health hazards among animal handlers is the development of laboratory animal allergy. There is no formal written legal requirement defines in details that employers shall establish and maintain the occupational health program among workers in the animals care facilities. Nevertheless, the general duty clause of Occupational Safety and Health Act 1994 (OSHA) mandates all employers to maintain the safety, health and wellbeing of the employees at workplace. Therefore it is the responsibility of the employers to maintain good occupational safety and health management practice in order to provide appropriate occupational health program to all high risk workers. The necessity of the development of occupational health program is also well elaborated in the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 2011). In addition, the guidelines described the occupational safety and health program designed for the animal facilities workers to be depending on the extend of hazards posted by the animals; the intensity , frequency and duration of exposure; the individual susceptibility as well as the incidence rate of occupational injury or ill health. Workplace hazard identification, risk assessment and risk control (HIRARC) had rated animal allergen as a major hazard during various tasks such as handling the animals' soiled bedding, feeding , breeding as well as in contact with their body fluid. Chronic exposure to those animal allergen may leave significant health impacts on the exposed workers, as worst as occupational asthma or chronic lung impairment. Taking into considerations the

intense likelihood of exposure, the risk posted among animal facilities' workers were rated as moderate to high. Furthermore, in-house data and statistic showed none of the positive LAA cases being notified or reported to the organizational Occupational Safety and Health Unit, most likely due to lack of awareness among the affected workers, unable to identify positive LAA symptoms, inadequate supervision, training and education, as well as they were unsure of the platform and mechanism to lodge the report.

The risk for animal allergy is associated with the nature of exposure. Hence, it is crucial to monitor the health status of workers exposed to laboratory animals in order to prevent significant allergies or occupational asthma. Clinical studies in the past revealed that continuous exposure to sensitizing and allergenic agents will result in chronic loss in lung function (Paggiaro et al., 1994; Venables, & Chan-Yeung, 1997), secondary to the chronic low level inflammation followed by repeated exposure. This was evidently supported by several studies conducted among the laboratory animal workers which reported that exposure to laboratory animal allergen is significantly associated with lung function decline (Renstrom, Malmberg, Larsson, Larsson, & Sundblad, 1995; Fuortes et al., 1997). Portengen and colleagues reported that exposure to laboratory animal allergen had been identified as a risk factor contributing to expedited airflow obstruction (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Altogether these findings postulated that the lung function may decline among the population exposed to allergen, typically in those with work related respiratory allergic diseases.

The active clinical survey holds the value of identifying all the incident cases of LAA in a particular workplace therefore set as fundamental in the establishment of control measures to reduce the incidence of sensitization by reducing overall exposure of workers to either animal allergen or animal related dust. This proactive measure provides extra advantages when compare to the passive surveillance which is fully relying on reporting from employees (Stave, & Darcey, 2012) ; and therefore necessitates present study in order to generate empirical data on LAA among animal facilities workers who exposed to laboratory animal allergen .

This study held the value to expand the theory on LAA among the exposed population besides provided the body of knowledge on the associated risk factors of LAA. There was limited research being conducted among the workers exposed to laboratory animals worldwide while majority of the studies were carried out decades ago. Therefore, the empirical gap existed between the findings generated in the past and the most recent status of LAA among the risky group could be demonstrated in this study.

1.3 Research Questions

Based on the preceding discussion, this study seeks to provide insight for the following research questions:

1. What is the prevalence of Laboratory Animal Allergy (LAA) among the animal facility's workers in a research institute in Malaysia?
2. Is there a significant association between the development of Laboratory Animal Allergy (LAA) symptoms and the occupational exposure to laboratory animals (compared to the control group)?
3. Is there a significant association between the declined lung function and the occupational exposure to laboratory animals (compared to the control group)?
4. Is there a significant association between self-reported LAA symptoms and the declined lung function?
5. Among the exposed subjects, is the magnitude of exposure (duration and frequency of exposure) an associated risk factor for the development of Laboratory Animal Allergy (LAA)?
6. Among the exposed subjects, is the job description (Handlers or users) an associated risk factor for the development of Laboratory Animal Allergy (LAA).
7. Among the exposed subjects, is the type of work area (Laboratory or Animal room) an associated risk factor for the development of Laboratory Animal Allergy (LAA)?
8. Among the exposed subjects, is compliance to Personal Protective Equipment (PPE) an associated risk factor for the development of Laboratory Animal Allergy (LAA)?
9. Among the exposed subjects, is atopy an associated risk factors for the development of Laboratory Animal Allergy (LAA)?

10. Among the exposed subjects, is being a smoker an associated risk factor for the development of Laboratory Animal Allergy (LAA)?
11. Among the exposed subjects, is owning of home pets an associated risk factor for the development of Laboratory Animal Allergy (LAA)?

1.4 Research Objectives

The present study aims to explore the relationship between the development of Laboratory Animal Allergy (LAA) with the lung function decline and various occupational exposure factors; therefore the research set the objectives as following:

1. To determine the prevalence of Laboratory Animal Allergy (LAA) among the animals facility's workers in a research institute in Malaysia.
2. To determine the association between the development of Laboratory Animal Allergy (LAA) symptoms and the occupational exposure to laboratory animals .
3. To determine the association between the lung function declined and the occupational exposure to laboratory animals .
4. To determine the association between self-reported LAA symptoms and the declined lung function.
5. To determine the associated occupational risk factors (duration and frequency of exposure, job description, type of work area, PPE compliance) and individual risk

factors (atopy, smoking status, owning of home pets) for the development of Laboratory Animal Allergy (LAA).

1.5 Scope of the Study

This study was conducted in a medical research institute in Malaysia in year 2019. All employees working in the research animals' facility were recruited as exposed group except for those who does not fulfill the inclusion criteria or meet the exclusion criteria (refer Inclusion/ Exclusion criteria in Chapter 3). Similar number of workers, who do not exposed to the laboratory animal allergens at any time, were recruited as the controlled respondents. The Laboratory Animal Allergy (LAA) was examined by employing specifically designed questionnaire while the lung function was investigated utilizing spirometer. The self-reported symptoms of LAA and lung function was compared between the exposed group and the control group, followed by the exploration of occupational exposure risk factors .In addition, the influence of confounders including smoking habit as well as home pet will also be identified.

1.6 Significance of the Research

This study focuses on the Laboratory Animal Allergy (LAA) and the lung function decline by examining various occupational exposure risk factors including type of animal handled, duration and frequency of exposure, PPE accessibility and usage, type of work area and history of atopy. The present case-control study examines the difference of LAA symptoms and the lung function decline between exposed group

and the controlled group. Therefore, the expected theoretical and practical importance is declared as following:

1.6.1 Contributions to the knowledge

The present study holds the importance and value of enhancing empirical data and about Laboratory animal allergy among the high risk exposed population in Malaysia. The data related to the topic of LAA remains limited among the Malaysian Laboratory animal workers. Hence, the updated data generated in this study which presents a picture of LAA prevalence and its associated risk factor in one of the research institution in Malaysia, is definitely useful as a baseline reference for future expanding study nationwide.

1.6.2 Practical Importance

This clinical survey is important in identifying the prevalence of LAA among the workers in the research animal facility, together with its occupational risk factors. The findings will provide a guide in order to design the comprehensive occupational health program. The LAA prevention should be the primary goal of a successful safety and health program in the workplace handling with research animals. The program can be accomplished by the changes in facility design, exposure reduction, education and training among the risky employees.

Early recognition of LAA symptoms also results in series of interventions with the ultimate aim to avoid or minimize the chronic health consequences. Hence, it ensures early treatment and rehabilitation with an excellent prognosis. Besides, the active clinical surveillance program will definitely play a crucial role in improving health status of the employees working with laboratory animals (Bush, Wood, & Eggleston, 1998). LAA is a preventable occupational hazard. One study revealed the LAA incidence of 10.3% among workers exposed to laboratory animals in a pharmaceutical company. Nevertheless, the prevalence was successfully reduced to zero following a comprehensive occupational safety and health program consisted of a number of environmental control measures in order to reduce the allergen exposure (Fisher, Saunders, Murray, & Stave, 1998). Therefore, knowing the existing prevalence of LAA together with its risk factors is an extremely important stepping stone for the development and implementation of future occupational safety and health prevention program.

Identification of the individuals who are at risk is an essential goal of the screening program. On the other hand, it can also help identify the personnel with preexisting allergies or asthma unrelated to occupational exposure. This assessment, although cannot be legally utilized as the criteria to preclude workers, however holds the value in task assignment which substantially minimize the exposure level towards animal allergen. The employees with predisposing sensitization to laboratory animal should have given the low-risk assignments. In addition, this study serves as a baseline data to identify sensitization in workers who might later develop LAA symptoms. Apparently,

individuals with known sensitivity to laboratory animal must avoid repetitive and chronic exposure besides closely monitored for the development of chest symptoms. It serves as an additional valuable point for the prevention of permanent disability following chronic negative health impacts.

1.7 Operational Definitions

1.7.1 Laboratory Animal

A wide variety of mammalian species used in the laboratory experimental study for medical research, such as mice, rats, rabbits, guinea pigs, hamsters, dogs, cats, pigs, cows, horses, sheep and monkeys. The rodents group including mice and rat are the most widely used species in medical laboratory research worldwide (Bush, Wood, & Eggleston, 1998).

1.7.2 Laboratory Animal Allergy (LAA)

LAA is the self-reported allergic symptoms following the exposure to at least one occupational allergen from the animal source such as rat, mouse, hamster, guinea pig or rabbit, and at the same time exhibit clinical symptoms over chest, nose, eyes and skin provoked by animals exposure somehow show improvement upon exposure reduction, supported by the clinical tests (Venables et al., 1988).

1.7.3 Allergen

An allergen is any harmless substance, most often eaten or inhaled, that is recognized by the immune system and triggers a response that starts in the immune system and results in an allergic reaction, causing the symptoms in nose, throat, eyes, ears, skin or roof of the mouth. The common allergens include dust mites, animal dander, mold, medications, insect venoms and various foods (American Academy of Allergy, Asthma and Immunology).

1.7.4 Sensitization

Sensitization is a process by which the immune system will produce a defensive protein, called an antibody, in response to any allergen it considers abnormal, and lead to a variety of allergic symptoms. It refers to the induction of an allergic response in the immune system (Janeway, Travers, Walport, & Shlomchik, 2001).

1.7.5 Atopy

Atopy is defined by positive history of atopic symptoms such as asthma, allergic disorder

involving skin, eyes and upper airway, which is strongly related with the LAA development (Fuortes et al., 1997; Kruize et al., 1997; Hollander, Heederik, & Doekes, 1997). It is a predisposition toward developing certain allergic hypersensitivity reactions and may have a hereditary component.

1.7.6 Pulmonary / Lung Function Test

Lung function tests are also known as pulmonary function tests. The word “pulmonary” refers to the lungs. They are a collection of tests that measure lung size and air flow, such as spirometry and lung volume tests, which are important to diagnose lung and airway diseases, and to identify the severity of pulmonary impairment (Burrows, 1975).

1.7.7 Spirometry

Spirometry (meaning the measuring of breath) is the most common pulmonary function tests. It measures lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. Spirometry is helpful in assessing breathing patterns that identify conditions such as obstructive and restrictive lung disease. Spirometry measures the rate of air flow and estimates lung size. It measures how much air you can inhale and exhale. It also measures how fast you can empty the air out of your lungs. Altogether it measures the values of FEV1, FVC and FEV1/FVC ratio (Miller et al., 2005).

1.7.7.1 Forced Vital Capacity (FVC)

This is the spirometry maneuver which begins with deep inhalation followed by exhalation of air as long and as forcefully as possible. The amount of air exhaled in

this manner is FVC. The reduction of FVC to below 80% suggests either obstructive or restrictive lung disease (Al-Ashkar, Mehra, & Mazzone, 2003).

1.7.7.2 Forced Expiratory Volume in one second (FEV1)

FEV1 is the amount of air exhaled forcefully during the first second following a FVC maneuver. It tends to be reduced to less than 80% in obstructive airway disease such as asthma (Al-Ashkar, Mehra, & Mazzone, 2003).

1.7.7.3 FEV1/ FVC Ratio

This ratio is being used to determine whether the pattern is normal, obstructive or restrictive. A value of less than 0.7 indicates obstructive pattern (Al-Ashkar, Mehra, & Mazzone, 2003)..

1.8 Organization of the Thesis

This thesis consisted of five chapters : chapter one, the introduction which highlighted the importance and necessity of present study ; chapter two, the literature review which discussed the significance and evidence reported in previous studies ; chapter three, the methodology which explained the study procedure and study protocol in details; chapter four , the results which reported the findings or outcome of the study following statistical analysis; finally followed by chapter five, the conclusion and recommendation which discuss the results of the study, the limitation and the

practical suggestions for the improvement besides drawing overall conclusion for the study.



CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Workers exposed to laboratory animals on regular basis were reported to have high risk of developing spectrum of allergic disorder, more commonly the respiratory allergies. Laboratory animal allergy (LAA) which may progressive into occupational asthma represent one of the major occupational illness especially for the population exposed to experimental animals such as laboratory technicians, veterinarian, physicians, researchers, scientist and also animal caretakers whose work requires frequent exposure (Bush, Wood, & Eggleston, 1998).

Research laboratory had been identified as a risky environment for the allergies development among the users (Taylor, Longbottom, & Pepys, 1977; Harries, & Cromwell, 1982). Rodents (mice and rats) are among the most abundantly used laboratory animals in medical research therefore are generating most common allergic disorder clinically (Bush, Wood, & Eggleston, 1998). These animals persistently shed allergens in form of protein substance through secretions likes body waste, urine, saliva, dander, hair as well as skin desquamation. As a result, these allergens deposit on the laboratory equipment or material besides retained in the air hence lead to skin and respiratory illness. Once workers developed sensitization towards specific allergens, continued exposure may lead to progressive and chronic loss to lung

function secondary to occupational asthma (Paggiaro, 1994; Venables, & Chan-Yeung, 1997). In line with these, several studies among laboratory animal workers were also demonstrated that exposure and sensitization to laboratory animal allergens significantly associated with lung function decline (Renstrom, Malmberg, Larsson, Larsson, & Sundblad, 1995 ; Fuortes, 1997).

2.2 Laboratory Animal Allergy (LAA)

2.2.1 Definition of LAA

LAA, a form of occupational sensitivity, is the presence of self-reported symptoms from the exposure to laboratory animals. It can be categorized into general LAA (without specific species) or species LAA (with specific species identified through serological evidence of sensitization). The presence of allergic symptoms had been utilized as the diagnostic criteria of LAA in many studies. An individual is considered to develop LAA if he/ she found to be sensitized to at least one occupational allergen from the animal source such as rat, mouse, hamster, guinea pig or rabbit, at the same time exhibit clinical symptoms over chest, nose, eyes and skin provoked by animals exposure and show improvement upon exposure reduction (Venables et al.,1988). The chest symptoms are wheezing, shortness of breath and chest tightness; nose symptoms are itchy, stuffy, blocked or runny nose in the absence of cold; eye symptoms are itchy and watery eyes while skin symptoms are itchy skin lesion typically in form of bumps excluding insects' stings. Those symptoms are secondary to exposure to one or more

animal species or their body fluids or tissue at work. The work related symptoms of LAA typically improved during weekends, vacation or after the exposure to animals been eliminated or minimized (Venables et al.,1988).

The occupational sensitization to animal allergen is highly associated with the clinical manifestation of skin reaction, rhinitis, and conjunctivitis; and might be as worse as asthma (Renstrom, Malmberg, Larsson, Larsson, & Sundblad, 1995). Rhinitis is defined as the experience of symptoms of blocked nose or runny nose in the absence of cold .Conjunctivitis means the presence of redness and irritation of eyes. Asthma is the clinical manifestation of groups of symptoms including shortness of breath, chest tightness and wheezing during the day or night.

2.2.2 The incidence and prevalence of LAA

The particle size of the animal allergens are extremely small therefore are easily airborne and inhaled, resulting in respiratory symptoms, itchy eyes and skin irritation. Multitude cross-sectional study constantly reported that the prevalence of LAA development ranging from 10% to 46% (Aoyama et al.,1992) ,others estimated the prevalence of 10%- 23% (Lutsky, & Neuman, 1975; Hollander, Doekes, & Heederik, 1997), depending on the laboratory setting and also the nature of exposure; while the allergic symptoms progress from mild rhinitis to a severe yet life threatening asthmatic episodes (Agrup, Belin, Sjöstedt, & Skerfving, 1986 ; Aoyama et al.,1992). In homogeneous with this finding, the prevalence rate over 40% had also been reported

for LAA (Venables et al., 1988). On the other hand, Ferraz et al. (2013) reported the occupational sensitization prevalence of 16% and 3 % between animals' handlers and non-handlers respectively in one study exploring the correlation between laboratory animals with respiratory allergies. The National Institute for Occupational Safety and Health (NIOSH) Boston estimated the prevalence of 33% of laboratory animal handlers develop allergy symptoms, with the most usual manifestations of stuffy or runny nose. In addition, approximately 10% of the animal handlers will eventually develop work-related asthma at later stage. The estimation of 70-80% of symptomatic workers was reported to have upper airway symptoms (Aoyama et al., 1992; Bush, Wood, & Eggleston, 1998).

Majority of the LAA development occurred within the first three years of exposure (Botham, Davies, & Teasdale, 1987), with nasal symptoms which rhinitis is being the first to appear. Those symptoms typically appear rapidly within minutes after the exposure. The latency period which is the duration from the exposure initiation until the onset of symptoms may vary from month to years, with the mean interval of 2 to 3 years (Gordon, Bush, & Newman Taylor, 2006). However workers who do not manifest symptoms within the first three years of contact are remaining at risk (Culinan et al., 1994).

2.3 Risk factors for LAA

2.3.1 Individual susceptibility

The individual susceptibility normally has a component of genetic basis. The association between LAA and atopy is well known (Slovak, & Hill, 1981; Cockcroft, McCarthy, Edwards, & Andersson, 1981). Atopy is defined by positive history of atopic symptoms such as asthma, allergic disorder involving skin, eyes and upper airway, which is strongly related with the LAA development (Fuortes et al., 1997; Kruize et al., 1997; Hollander, Heederik, & Doekes, 1997). It is a predisposition toward developing certain allergic hypersensitivity reactions and may have a hereditary component. The relationship in between positive family history of atopy (among first order relatives such as parents, siblings and children) and the LAA development had been demonstrated in some studies. Individual with atopy are nearly 11 times more likely to become sensitized to the animals allergen (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Venables et al. (1988) postulated the association between atopy and chest symptoms, in which chest symptoms were reported five times more common among atopic subjects compared to their non-atopic counterparts. Besides, workers with background of atopics reported to have shorted latency period than non-atopic workers in the symptoms manifestations (Kruize et al., 1997).

There was significant association between smoking and LAA chest symptoms (Venablers et al.,1988). It would not be surprising if smoking were related to LAA as the inhalation of tobacco smoke will potentiate the to the sensitization process (Zetterstrom, Nordvall, Björkstén, Ahlstedt, & Stelander, 1985).It was also evidently demonstrated by literature that smoking is a risk factor for occupational allergy , possibly by enhancing the transportation of antigen (Venables et al.,1985). Besides, the history of smoking evidently reduced the lung function compared to non-smoker (Fuortes et al.,1997).

Moreover, some other non-occupational exposure to animals especially home pets, may confound the relationship between LAA and work-related exposure. Pets like cats and dogs were found to be an important risk factor for LAA (Hollander, Doekes, & Heederik, 1997).

2.3.2 Occupational exposure

The animal allergens will become airborne during variety of laboratory procedures such as animal handling, cages cleaning, feeding and the change of animal bedding, breeding and even dosing or experimental procedure. As a result, the laboratory employees are at high risk of exposure via inhalation and dermal contact, which had been identified as the primary route of entry for animal allergen (Harrison, 2001).

Laboratory animal handlers and users were both reported to have higher likelihood to develop LAA symptoms compared to the non-exposed population (Venables et al.,1988). Ample studies had documented that the sensitization to laboratory animal as well as the risk of symptoms development actually increased with the duration of exposure, the airborne concentration of allergen (Gordon, Bush, & Newman Taylor, 2006), type of animals and also the number of species handled. In addition, peak exposure of short duration might be more hazardous compared to average exposure. The exposure-response relations had been agreed by several studies. The chest and skin allergy symptoms were found to be related to exposure indices including intensity of exposure among workers with different job titles (Cullinan et al., 1999 ; Nieuwenhuijsen et al.,2003). The intensive exposure were experienced by animal handlers, compared to those scientists or laboratory assistants who are exposed to low level but prolonged contact (Bland, Levine, Wilson, Fox, & Rivera, 1986). Elliott, Heederik, Marshall, Peden, & Loomis (2005) also reported that animal care workers had the highest rate ratio for developing LAA symptoms while scientists and laboratory technicians exhibited lower risk. The exposure is very much associated with the task performed where duty requires exposures to cages or different animals at one time evidently increased the risk ratio with duration of exposure (Pacheco et al.,2006 ; Nicholson, Mayho, Roomes, Swann, & Blackburn, 2010 ; Harrison, 2011). Inversely, laboratory work such as dosing and experimentation do not require working with many animals at one time, therefore had lower risk for LAA. Indirect contact such as working near the animal cages or bedding and even in contact with the dirty laboratory coats is also one of the risk factors. On the other hand, the nature of the

allergens or in other word the type of animal is an important determinant in the exposure-response relations between animal allergens and the development of allergic symptoms, in order to ascertain the potency for sensitization (Gautrin, Ghezze, Infante-Rivard, & Malo, 2000). Employees who developed allergic reactions towards one animal species might at risk of developing allergy to other species (Goodno, & Stave, 2002).

2.4 Assessment of Laboratory Animal Allergy (LAA)

2.4.1 Assessment of occupational history

The primary tool in diagnosing LAA is the comprehensive occupational medical history (Bush, 2001) which is aided by specifically designed and comprehensive questionnaire (Bernstein, Campo, & Baur, 1999 ; Seward, 2001). Nevertheless, there was no standardized questionnaire for the LAA diagnosis. The mandatory information should include socio-demographic data, present and past employment history, a thorough occupational history on laboratory animal contact; the nature of task, duration and frequency of contact, presenting symptoms including the onset and severity of symptoms with its correlation to the exposure in animal facilities (Bernstein, Campo, & Baur, 1999).

It is extremely important to determine in the medical history if there is relation between symptoms experienced before , during and after exposure to specific allergen

at the workplace (Malo, & Chan-Yeung, 2001). LAA usually improved over weekends or when workers away from the source of exposure. However, the diagnosis of LAA should not be underestimated if the symptoms found to be no improvement when worker away from work, as when chronic inflammation can occur when it progressed into severe stage due to persistent exposure (Park & Nahm,1997). In addition, the home environment and past medical history should also be included in the questionnaire: smoking history, domestic furry pets, preexisting history or allergic reaction (allergic rhinitis, dermatitis or asthma) and positive family history of allergic disorders.

2.4.2 Assessment of Pulmonary/ Lung Function

Clinically relevant airway obstruction can be the impact of continuous exposure to laboratory animal allergen over few years, and even worse among the sensitized population. However, lung function impairment may also occur in the absence of prominent LAA (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). The lung function assessment is crucial for the confirmation if laboratory animal allergen induced asthma is suspected, besides measuring the degree of lung impairment (Bush, 2001) using spirometry.

Spirometry is the measurement of the air movement into and out from the lung during different respiratory maneuvers, in order to detect the volume of air can be inhaled or exhaled together with its speed. It is the gold standard for lung function examination

as the changes of lung function had been reported to be directly proportional to the extent of exposure to laboratory animal allergen (Enarson, & Yeung, 1985). Lung function assessment should be performed among workers complaint of lower respiratory tract symptoms likes cough, shortness of breath, wheezing and chest tightness upon animals contact. Nevertheless, Spirometry also found to be advantageous in detecting subclinical asthma while workers only presented with upper airway symptoms such as nasal congestion, runny nose, itchy nose and sneezing, or whenever laboratory animal allergen induced asthma is suspected (Malo, & Chan-Yeung, 2001).

Workers who experienced LAA during or shortly after working with laboratory animals tended to have decline lung function with significant airflow obstruction compared to those without allergic symptoms (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Besides, significant lung function decline was also found among laboratory animal workers with less than four years occupational contact ,who were sensitized with continuous exposure (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003 ; Gordon, & Preece, 2003). The exhibition of significant obstructive pattern from the lung function test typically indicates the possibility of occupational asthma.

2.5 Prevention of LAA and Management of exposure

2.5.1 Exposure avoidance

LAA has an excellent prognosis if the exposure is avoided at early stage. Avoidance of the exposure had been identified as the primary treatment (Bush, 2001). Removal of workers from continued exposure is important once the diagnosis of LAA had been confirmed (Bernstein, 2016). Detecting occupational illness with medical attention given at an early stage is of paramount importance, as delay in diagnosis will adversely affect the prognosis (Yeung, & Grzybowski, 1985), and workers are less likely to recover completely if the diagnosis is made late. Majority of the LAA symptoms were mild. Nonetheless, prolonged exposure without preventive action might permit the symptoms to eventually progress into chronic defect with long term health impact.

2.5.2 Exposure Reduction

Minimizing exposure to allergen is essential in order to prevent the progression of sensitization and development of allergic symptoms (Bush, Wood, & Eggleston, 1998). The goal of reducing exposure is to minimize the frequency of sensitization among laboratory animal workers. The exposure reduction can be achieved through various control measures as per suggested in the hierarchy of control: substitution, engineering control, administrative control and personal protective equipment (PPE).

Female rats that are proven to excrete less protein allergen in their urine are highly suggested to be used in laboratory experiments as a substitution. In addition, attention to the design of facility and equipment in corporate with multiple engineering control can be employed such as the use of biological safety cabinets, local exhaust ventilation (Harrison, 2011), filtered top cages, ventilated caging (Schweitzer et al., 2003) and negative pressure environment. Administrative control involves the provision of separate lockers for clean clothing, shower room, training, information, instruction, supervision, safe operating procedure, education, medical surveillance program, pre-placement policy, housekeeping, standard handling method and restricting access to animal facilities. The utilization of PPE is extremely crucial especially for the task with greatest requirement such as cage cleaning which is known to generate peak levels of airborne animal allergens.

2.6 Summary

Laboratory animal allergy (LAA) is an acknowledged occupational hazard which might in later stage leave impact on health outcome as well as career. Its symptoms can be ranging from mild skin irritation to severe and chronic asthma. The elimination of source of allergen for highly vulnerable group and also effective reduction in exposure are the desired goals to minimize the incidence of LAA, as continuous exposure after onset of symptoms will increase the likelihood of irreversible disorder. An effective LAA prevention program should have combined the components of engineering control, administrative control and PPE. On the other hand, the prevention

of the LAA developments among the exposed workers should be set as the golden aim for all facilities engaged in the utilization of laboratory animals.



CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Introduction

This chapter aims to describe the methodology employed in this study, especially the study design and study protocol utilized in order to obtain the empirical information and evidence to ensure the research objectives are utterly met. The independent variables and dependent variables to be investigated are visibly defined in this chapter. In addition, the minutiae of the reliable study instruments, procedure and protocol which are employed to measure all variables will be explained in this chapter, completed with the data collection procedure and statistical analysis.

3.2 Theoretical Framework

Theoretical framework is defined as a conceptual model to demonstrate the relationship or association among multiple factors that had been identified as important variables to be investigated in a study (Sekaran, & Bougie, 2016). The present study was performed to examine the incidence of Laboratory Animal Allergy (LAA) and lung function decline among the animal facilities' workers in a research institute, comparing to the non-exposed or controlled group, together with its associated factors. The overall study model is illustrated in Figure 3.2. The

independent variables exhibit some extend of influence on the dependent variable in either positive or negative way. The independent variables in present study were appointed as two: the exposed group consisted of the research animal facilities' workers, and the controlled group made up of respondents without direct occupational exposure to the animal allergen. Within the exposed group, the associated occupational risk factors were examined including the magnitude of exposure (duration and frequency of exposure), the type of work area, compliance to the usage of personal protective equipment (PPE) and history of atopy. On the other hand, the dependent variables are self-reported symptoms on occupational allergy reaction to animal allergen, supported by the pulmonary/lung function value.



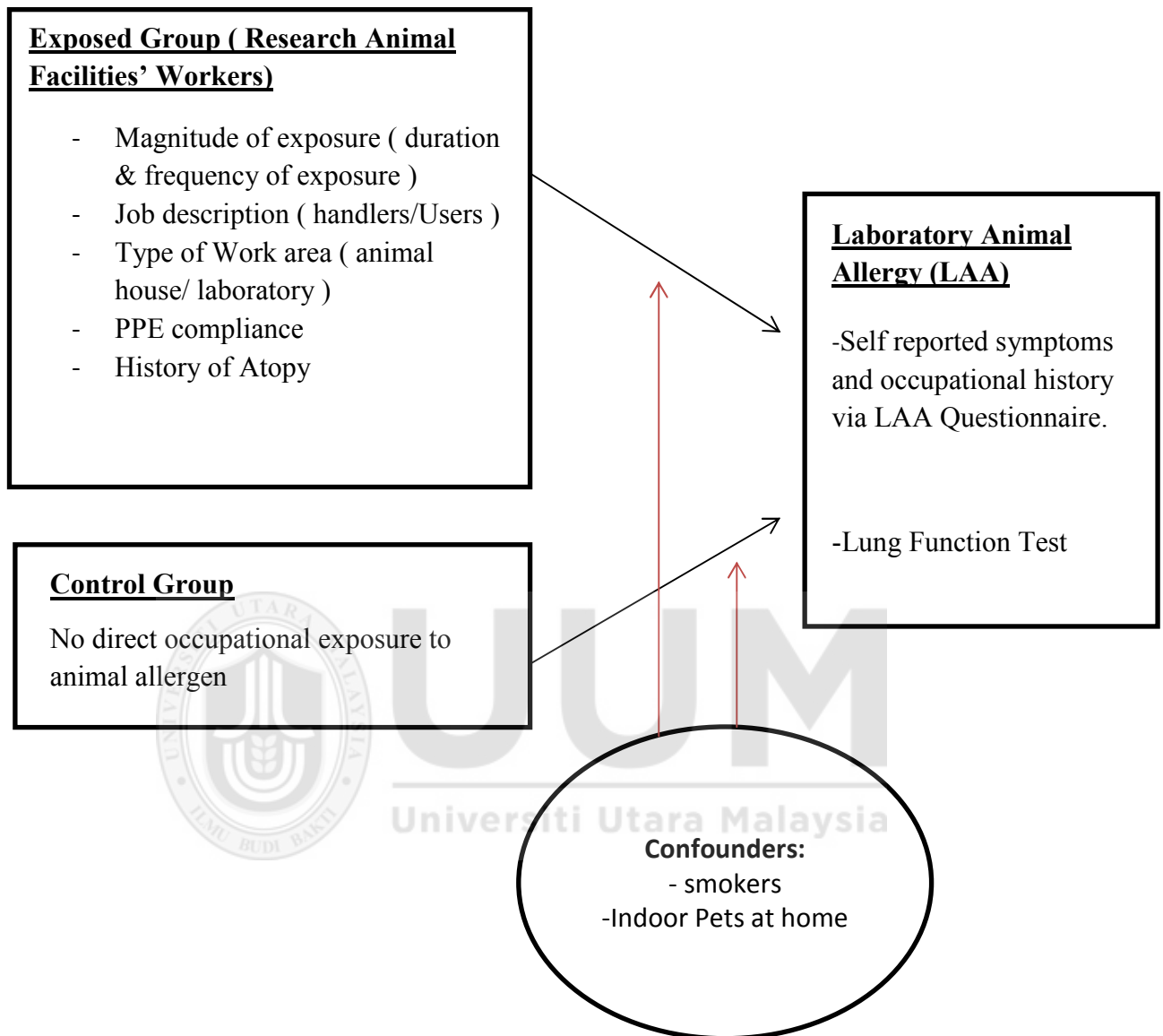


Figure 3.2
Theoretical Framework

3.3 Research Hypotheses

The study hypotheses were developed referring to various literature, in order to enable the relationship testing among the variable examined.

- H1a: The exposed group is significantly more likely to develop Laboratory Animal Allergy (LAA) symptoms compared to the controlled group.
- H1b: The exposed group is significantly more likely to have declined lung function compared to the controlled group.
- H2: There is significant association between Laboratory Animal Allergy (LAA) symptoms and the declined lung function.
- H3: Among the exposed group, workers with higher magnitude of exposure (duration and frequency) are more likely to develop Laboratory Animal Allergy (LAA) compared to those with lower magnitude of exposure.
- H4: Among the exposed group, animal handlers are more likely to develop Laboratory Animal Allergy (LAA) compared to the animal users.
- H5: Among the exposed group, workers working in animal room are more likely to develop Laboratory Animal Allergy (LAA) compared to those who works in the laboratory
- H6: Among the exposed group, workers comply to full PPE are more likely to develop Laboratory Animal Allergy (LAA) compared to those who do not comply.

- H7: Among the exposed group, workers with atopy are more likely to develop Laboratory Animal Allergy (LAA) compared to non-atopic.
- H8: Among the exposed group, workers reported positive smoking status are more likely to develop Laboratory Animal Allergy (LAA) compared to non-smokers.
- H9: Among the exposed group, workers who own home pets are more likely to develop Laboratory Animal Allergy (LAA) compared to those without home pets.

3.4 Research Design

3.4.1 Nature of the Study

This is a quantitative study which consisted of systematic empirical investigation of the observable phenomena via statistical, mathematical, or computational techniques (Given, 2008). In natural sciences and social sciences, quantitative research holds the objective to develop mathematical models, theories and hypotheses pertaining to phenomena. The measurement process is central to the quantitative research because it provides the fundamental connection between empirical observation and mathematical expression of quantitative relationships. Quantitative data is any numerical data that will be analyzed with the aid of statistics in order to generalize the unbiased result to some larger population.

3.4.2 Study Purpose

The present research fulfills the design of analytic study which is specifically used for hypotheses testing. Samples of subjects are identified and information about exposure status and outcome is collected. The essence of an analytic study is that groups of subjects are compared in order to estimate the magnitude of association between exposures and outcomes. This study is also descriptive in describing the occurrence of Laboratory Animal Allergy (LAA) and lung function decline among the animal facilities' workers in a research institute, comparing to the non-exposed or controlled group; while among the exposed group, the significance of each occupational risk factor was investigated to substantiate the relationship between LAA and its associated risk factors.

3.4.3 Study Time Horizon

This is a cross-sectional evaluation of the animal facilities' workers exposed to the laboratory animals, with the non-animal handler employees used as the control group, conducted from the study period of 1 January 2019 through 30 Mei 2019. Cross-sectional study is a type of observational study that analyzes data from a population, or a representative subset, at a specific point in time. Cross sectional study falls under category of observational study in which the study population will be observed without interference by the investigator.

3.4.4 Unit of Analysis

The unit of analysis is the major entity that being analyzed in a study. It is the 'what' or 'who' that is being studied. In present research, each respondent was analyzed individually as every study subject represents himself / herself.

3.5 Instruments and Measurements

3.5.1 Laboratory Animal Allergy (LAA) Questionnaire

The primary tool to diagnose LAA is the comprehensive occupational medical history (Bush, 2001) which is aided by specifically designed LAA questionnaire (Bernstein, Campo, & Baur, 1999; Seward, 2001). The important elements that must be included in the questionnaire are information about present and previous job for the individual workers, the nature of work task, exposure indices, and patterns of LAA symptoms together with the potential risk factors which precipitates the LAA development. These key components of the occupational history that are compulsory to be included for the evaluation of occupational allergic reactions were adapted from Bernstein (2016).

There are multiple sources of LAA questionnaire such as the simplified version proposed by Seward (2001), Bush (2001), and also the integrated version developed by Bush, Wood, and Eggleston, (1998). The questionnaire employed in this study is adapted from Bush, Wood, and Eggleston, (1998) which is found to be more

comprehensive, systematic and precise. However, all items are further arranged in a more organized flow consisted of 6 sections: Part A to Part F, with a total of 28 main items.

Part A the socio-demographic information contains six items namely name, age, gender, race, address and educational background of the respondents. Part B the employment history comprises of four items: the job title, duration of employment in current job, previous exposure to laboratory animals before current employment and details about past occupational exposure if applicable. The categorization of job description is useful as proposed by Cockcroft and colleagues (1981), in which laboratory workers are divided into two main category: the handlers (animal care takers who are responsible for the cage cleaning, feeding and provide care for animals) and users (those involved in experimental use of the animals such as technicians, students and scientists). Part C with a total of four item consisted of information regarding present job on the type of work area (animal house or laboratory) and also the nature of contact whether the subjects involve in direct handling with the animals' tissue or secretion and even the contaminated equipment. Recent exposure to the laboratory animals was defined as self-reported contact with the laboratory animals or even their excretions likes blood, urine and stool, in the past 12 months (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003).

Part D contains occupational history on the contact or exposure to laboratory animal allergen. This part is divided into three main items. Item 1 describe the duties and

nature of work (handling stool or urine, blood collection, tissue harvesting, surgical procedure, dissection, handling soiled bedding, feeding, breeding, cage cleaning, carcasses handling and injecting the animals. Item 2 specifies the type of animal handled (mouse, rat, hamster, guinea pig, rabbit, goat, monkey, cat or others), together with the exposure indices which is the duration and frequency of contact. The duration of contact will be expressed in years, whereas the frequency of contact will be clarified as daily contact (with specific hours per day), at least once a week (with specific hours per week) and less than once a week (with specific hours per month). Next, item 3 clarifies the compliance to personal protective equipment (PPE). Exposed workers need to justify the accessibility of PPE at their workplace and whether they utilize PPE at all time.

Part E (3 items) of the LAA questionnaire requires subjects to report the present symptoms upon contact with laboratory animals. These symptoms including water or itchy eyes, swollen eyes or lips, skin rashes or itchiness, stuffy or congested nose, runny nose, sneezing, cough, wheezing, shortness of breath, chest tightness and asthmatic attack. Respondents will need to specify the year of onset and either those manifestation of symptoms occur at work, at home, on vacation or no difference regardless of location. In addition, subjects who reported LAA symptoms must clarify the duration of how soon those symptoms started after the exposure to laboratory animals, besides the duration that those symptoms last. The duration being categorized into four: less than 10 minutes, 10 minutes to 1 hour, 1 hour to 8 hours, and more than 8 hours.

The final part of the LAA questionnaire is completed with the home environment or past health information including the indoor pets, smoking status and atopy (previous allergic reactions or asthma running in the subject or among the blood of kin such as grandparents, parents and brothers/ sister). This section is essential to rule out the individual susceptibility which might be the predisposing factor for the development of LAA.

All subjects in the exposed group were required to complete from Part A until Part F, while those in control or non-exposed group were only required to fill up Part A, B E and F. All of the subjects possess adequate English literacy and proficiency that they have the ability to read and understand English therefore the original English version of questionnaire was employed without translation into Bahasa Malaysia.

3.5.2 Spirometry

The LAA questionnaire, although possess high sensitivity somehow less specific with confirmatory clinical testing which is more objective in heading towards the diagnosis of LAA. Malo and Chan-Yeung (2001) reported the poor correlation between the history obtained from the questionnaire and the diagnosis as confirmed by other specific clinical test. This justified the need of combining LAA questionnaire along with the lung function test in order to answer the research questions.

Spirometry which is one of the test falls under lung function test, was performed using spirometer, which is an apparatus for measuring the volume of air inspired and expired by the lungs. A spirometer measures ventilation, the movement of air into and out of the lungs while spirogram is the graphical picture which will identify two different types of abnormal lung patterns: obstructive and restrictive. Spirolab III (comply to Operation Manual Code MIR 980067) was the spirometer used in present study. It was well calibrated prior to study and then daily throughout the study period. The values Forced Vital Capacity (FVC) , Forced Expiratory Volume at 1 Second (FEV1) and the ratio of FEV1/FVC were measured in the spirometry maneuvers. The important information likes age, gender, height and weight were keyed in for each individual before the test. This information is useful for the spirometer software to estimate the predicted normal value of FVC and FEV1 for every subjects and the measurement obtained from the subjects was then compared to the predicted value in the unit of percentage. Lung function change can be defined as the deviation of the value measured from the predicted normal value.

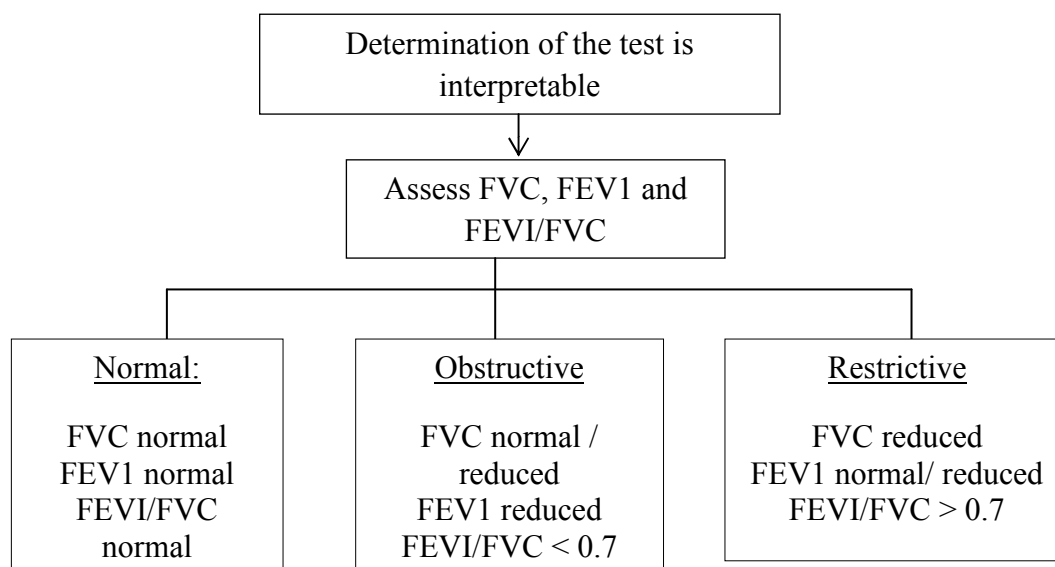


Figure 3.5.2
The interpretation of spirometry

3.6 Sampling

3.6.1 Target Population

All workers with potential exposure to the laboratory animal allergen were enrolled in this study as the exposed group. This animal-handler group built up with individuals working in the animal room or laboratory, including animal care takers, laboratory technicians, veterinarian, doctors and researchers; while the control group as known as non-animal handler group consisted of management and administration employees, secretaries and computer technicians who never have occupational exposure to the laboratory animal.

3.6.2 Inclusion and Exclusion Criteria

To recruit respondents in the exposed group, the inclusion criteria were subjects of both genders, age of 18 years and above, with the ability to understand and follow the instruction on study protocol, and also able to undergo the spirometry procedure. The exposed group only involved those actively working in the animal facilities in the past twelve months such as animal care takers, laboratory technicians, veterinarian, doctors and researchers. While for the control group, similarly selective criteria including subjects of both genders, age of 18 years and above, with the ability to understand and follow the instruction on study protocol, and also able to undergo the spirometry procedure but consisted those with no direct occupational exposure to the laboratory animal such as management and administration employees, secretaries and computer technicians.

The exclusion criteria for the two independent groups as follows: pregnant women and those with contraindication for the spirometry test (active tuberculosis, recent surgical procedures on eyes, chest and abdomen, and significant heart impairment).

3.6.3 Sample Size

Sample size was calculated using “PS Power and Sample Size Software”. This research is planning on a study of independent cases and controls with 1 control(s) per case referring to Ferraz et al (2013). Prior data indicated that the probability of

exposure among controls is 0.03, while the true probability of exposure among cases is 0.16 (Ferraz et al., 2013). Therefore we would need to study on 38 case subjects and 38 control subjects in order to reject the null hypothesis that the exposure rates for case and controls were equal with probability (power) of 90% or 0.9. The Type I error probability associated with this test of this null hypothesis set as $\alpha = 0.05$. However all the 87 workers who experienced occupational exposure to laboratory animal are included in this active clinical survey, yielding the total sample size of 174 (87 subjects in the exposed group and 87 subjects in the control group) based on the ratio of 1:1. Full recruitment primarily due to the health surveillance program is mandatory for all exposed workers in order to fulfill the requirements under the duties of employer under OSHA 1994. The significance of full recruitment was due to the aim of not missing any possible positive case of occupational allergy.

3.7 Data Collection

3.7.1 Data Collection Procedure

The research was conducted from the study period of 1 January 2019 through 30 Mei 2019, involving a total of 174 subjects (87 exposed population and 87 from the control group). The written permission from the top management of the organization was first obtained. Data was obtained through the self-administration of LAA questionnaire together with the spirometry test. For each subject, the completion of LAA questionnaire and the conduction of spirometry were both performed on the same day.

The investigator explained the objective and procedure of the survey to all subjects before initiation of the data collection and their participation was on a voluntary basis. They had the right to refuse to answer any question from the LAA questionnaire and could withdraw from the study at any juncture. In addition, respondents were assured that all information provided would be kept confidential and would be utilized for research purposes only. Written informed consents were obtained from the selected respondents prior to conducting the protocol.

All Spirometry procedures were conducted on Thursday and Friday in order to allow the lung function test to act as the plausible indicators of the workweek effects for the occupational exposure.

The equipment was cleaned, calibrated and well maintained prior to the use; and the calibration was carried out daily throughout the study period. All participants were asked to avoid caffeine consumption and smoking at least an hour before the lung function test, as well as to refrain from strenuous exercise 6 hours prior to the procedure. Besides, the abstained from using anticholinergic inhaler for 12 hours and oral medication for 24 hours before the procedure was also strictly applied (Crapo et al.,1995).

Spirometry was conducted by the trained occupational health practitioner, adhering to the lung function examination protocol practiced by the European Community Respiratory Health Survey. The demonstration of the correct technique was

performed before inviting subjects to use spirometer for their first time. The subjects were given some practice attempts before the exact reading were recorded. Next, the record of gender, age, height and weight were made for each subject so that the measurement of FEV1 and FVC could be compared with the predicted normal value. The spirometer will perform the calculations.

The clean, one way and disposable mouthpiece was attached to the spirometer and measurements were performed in standing position with the participants wearing nose clip. The subjects were instructed to breathe in fully and deeply, seal their lips followed by blowing the breath out forcibly until nothing left to expel. As much as three technically adequate maneuvers were allowed to be attempted for each subject, and the best results among the three would be recorded. If the investigator failed to be obtained three technically satisfactory results after eight attempts, the test would be terminated and rescheduled on other day. The references guides of Crapo (1995) were utilized in order to evaluate the findings.

3.7.2 Ethical Considerations

The written consent was obtained from all subjects upon recruitment. Procedure explained verbally and subjects are allowed to ask questions. Subjects were then made free decision to participate in the study. The privacy and confidentiality of personal information were maintained. All the investigators have no conflicts of interest related to the content of the study.

3.8 Pre Test

A pilot or preliminary study refers to a small-scale of a complete survey or a pretest for a particular research instrument such as a questionnaire or interview guide. Pilot studies could be conducted in qualitative, quantitative, and even mixed methods research. It is the pre-study of a fuller study. Its conduction is important in the evaluation of feasibility, time, cost, limitations and adverse events prior to the conduction of a full-scale research project (Thabane et al.,2010). A total of 30 respondents (15 exposed subjects and 15 controlled subjects) who were equally distributed by gender, were randomly selected to participate in the pre-test in order to identify any problems such as unclear wording or the questionnaire taking too long to administer the spironetry. No correction made and the findings resulted from pilot study were being brought into the actual study.

3.9 Data Analysis Techniques

All statistical analysis were performed using SPSS version 20 statistical software and results were presented with a 95% confidence interval (CI) and p-values of 0.05 for the statistical significance. Data cleaning were accomplished prior to data analysis.

3.9.1 Descriptive Analysis

The socio-demographic attributes of both groups of animal handlers and non-animal handlers along with data distribution were illustrated using descriptive analyses. Cross tabulation and Chi-square analysis were employed to describe self-reported LAA symptoms and presence of lung function decline between both the exposed and the control group.

3.9.2 Statistical test for two independent samples

The normality of the data was examined. The independent t-test was used for the normally distributed data while the Mann Whitney U-test was employed for non-parametric data. These analyses were used to compare the mean or median differences of the value of FEV1, FVC and FEV1/FVC between two independent study group namely the exposed group and control group. The mean or median differences between the two independent samples can be evaluated if the tested variables are numerical data with the group variable in form of categorical data. The parametric analysis of independent t-test was employed for Forced Vital Capacity (FVC) in view of the random samples, independent observations, adequate sample size of more than 30, equal population variances of the two groups and most importantly the data was normally distributed in each group. The normality test of Kolmogorov-smirnov showed that p value was significant >0.05 therefore the hypothesis for normality was accepted and the FVC data was normally distributed.

On the other hand, the non-parametric analysis of Mann-Whitney U Test was employed for Forced Expiratory Volume at 1 second (FEV1) and the ratio of FEV1/FVC in view of the assumptions for parametric test were not satisfied. Mann-Whitney U Test is the nonparametric alternative to independent t-test when the dependent variables in both groups were not normally distributed. The normality test of Kolmogorov-smirnov for both FEV1 and the ratio of FEV1/FVC showed that p value was insignificant <0.05 therefore the hypothesis for normality was rejected. The data of FEV1 and the ratio of FEV1/FVC were asymmetrically distributed and hence the median difference between groups will be evaluated rather than mean difference.

3.9.3 Multivariable Logistic Regression

The associations between positive LAA symptoms and lung function decline with the occupational risk factors that were listed as independent variables (duration and frequency of exposure, availability and usage of PPE, work area, job characteristic , history of atopy, smoking status and owning of indoor pet) were determined via multivariable logistic regression (MLR). The MLR was carried out by 'Enter method' to determine the 'real effect' of each independent variable with dependent variable, after controlling for the confounding effects of other independent variables.

3.10 Chapter Summary

Research methodology right from the determination of study design, study population, study location, sampling technique, the selection of study instruments and study procedure are extremely important to ensure that entire research protocol is conducted appropriately with legitimate. In addition, data analysis technique is imperative to ensure that the data integrity is the accurate and appropriate analysis of research findings in relation to the research questions, research objectives and hypotheses.



CHAPTER 4

RESULTS AND FINDINGS

4.1 Introduction

This chapter describes the results obtained from the data analysis utilizing statistical analytic methods in order to reach the research objective. This chapter illustrate the research findings which can be used to answer the research questions that being examined. All statistical analysis were performed using SPSS version 20 statistical software and results were presented with a 95% confidence interval (CI) and p-values of 0.05 for the statistical significance. Data cleaning were accomplished prior to data analysis. The socio-demographic features of the respondents were illustrated using descriptive analyses. Cross tabulation and Chi-square analysis were employed to describe the association between self-reported LAA symptoms and the lung function decline between both the exposed and the control group. The normality of the data on all lung function values was then examined. The independent t-test was used for the normally distributed data while the Mann Whitney U-test was employed for non-parametric data. The associations between the development of LAA and the occupational risk factors that were listed as independent variables (duration and frequency of exposure, availability and usage of PPE, type of work area, job description, history of atopy, smoking status and owning of indoor pet) were determined via multiple logistic regression (MLR).

4.2 Response Rate

A total of 174 LAA questionnaires were distributed to 87 exposed subjects in contact with laboratory animal allergen in Institute for Medical Research, IMR Kuala Lumpur and another 87 of control subjects made up of workers without direct occupational exposure to laboratory animals. All respondents were given adequate time to answer the questionnaire and it was then collected on the spot once the answering session had been completed. Full response rate of 100% was achieved (Table 4.2), as all high risk workers working with the laboratory animals were compulsorily involved in this clinical survey which is also a part of the workplace medical surveillance program according to the safety and health policy in order to maintain the safety, health and wellness of the workers to the optimum level.

Table 4.2
Response rate

Items	Exposed group	Control Group	Total	%
Distributed questionnaire	87	87	174	100
Collected questionnaire	87	87	174	100
Unreturned questionnaire	0	0	0	0
Completed questionnaire	87	87	174	100

4.3 Reliability and Validity Test

The complete version of questionnaire being employed in present study was adapted from Bush, Wood and Eggleston (1998). The present study was clinical survey with the survey tool made up of occupational exposure history with history of presenting symptoms in details however did not consisted of psychometric properties in the form of Likert Scale. None of the questionnaire's item was measuring the individuals' mental capabilities, behavioural style or cognitive abilities. Therefore both the validity and reliability test examining the internal consistency (Cronbach alpha value) and the correlation between items were not practical to be ran in this study. However, a pre-study as known as small scale pilot study involving 30 respondents (15 exposed subjects and 15 control subjects) had been carried out in order to evaluate the feasibility, time, cost, limitations and adverse events prior to the conduction of a full-scale research project. The pre-test was uneventful without any problem. The wording used in questionnaire was clear and timing given for the questionnaire administration and also the conduction of spirometry were sufficient. No correction being made and the findings resulted from pilot study were being brought into the actual study, combined and presented in the overall research results.

4.4 Sample Description

The present study investigated the development of Laboratory Animal Allergy (LAA) and the lung function declined between the working group exposed to laboratory

animals in their daily task, compared to the non-exposed population that acted as the control group. Each of the exposed group and control group were consisted of 87 subjects respectively, applying the one to one ratio. The socio-demographic distribution for all respondents in overall together with the illustration according to exposed group and control group is well displayed in Table 4.4.

In overall, taking into consideration of all subjects in both exposed and control group, majority of the respondents were female (59.2%) compared to male (40.8%). The Malay ethnic made up of 69.5% among all subjects. A huge proportion of subjects fall within the productive age group of 25-44 years old (73.6%) and achieved tertiary education attainment (79.9%). Approximately one-fifth (19.5%) from the total respondents reported atopy. Nearly One third (31%) of the overall subjects reported at least one positive LAA symptoms and presented with declined lung function (29.9%).

Focusing on the exposed group solely, more than half of the exposed subjects were female workers (57.5%). About three quarter of the animals facilities' workers were between 25-44 years (74.7%) and received tertiary level of educational attainment (79.3%). Almost one in five (18.4%) among them were current smokers. More than half (58.6%) of the exposed population were complaint of at least one LAA symptoms while 56.3% were found to have abnormal lung function as detected by lung function test. From the 87 subjects exposed to laboratory animals, about one fifth (21.8%) had history of atopy and approaching one quarter (24.1%) reported to own home pets.

On the other hand, the present study had also collected a total of 87 samples as control group. A major proportion was consisted of female (60.9%) , Malay ethnic (62.1%), came from the productive age group of 25-22 years old (72.4%) as well as attained tertiary education (80.5%). One fifth among the controlled respondents were current smokers (20.7%). Subjects without occupational exposure to laboratory animals somehow reported LAA symptoms were as little as 3.4%, whereas similar prevalence had also been documented for declined lung function (3.4%). Less than one fifth of the controlled population experienced atopy (17.2%) while one in ten was keeping pets at home (10.1%).



Table 4.4

Socio-demographic distribution with prevalence of LAA and declined lung profile

Variables	Overall		Exposed Group		Control Group	
Gender						
Male	71	40.8	37	42.5	34	39.1
female	103	59.2	50	57.5	53	60.9
Ethnic						
Malay	121	69.5	67	77.0	54	62.1
Others	53	30.5	20	23.0	33	37.9
Age group (years)						
Less than 25	4	2.3	2	2.3	2	2.3
25-44	128	73.6	65	74.7	63	72.4
More than 45	42	24.1	20	23.0	22	25.3
Educational level						
Secondary	35	20.1	18	20.7	17	19.5
Tertiary	139	79.9	69	79.3	70	80.5
Smoking status						
Non smoker	136	78.2	69	79.3	67	77.0
Ex smoker	4	2.3	2	2.3	2	2.3
Current smoker	34	19.5	16	18.4	18	20.7
Atopy						
Yes	34	19.5	19	21.8	15	17.2
No	140	80.5	68	78.2	72	82.8
Own of Home pets						
Yes	30	17.2	21	24.1	9	10.3
No	144	82.8	66	75.9	78	89.7
Presence of at least one LAA symptoms						
Yes	54	31.0	51	58.6	3	3.4
No	120	69.0	36	41.4	84	96.6
lung function						
Normal	122	70.1	38	43.7	84	96.6
Declined	52	29.9	49	56.3	3	3.4

4.5 Description on occupational risk factors among the exposed subjects

Among the 87 subjects who were exposed to laboratory animal allergen occupationally, the ratio of animal users to animal handlers was 7: 3. Animal users includes the laboratory technician, veterinarian, physician, scientist and researcher; while animal handlers were attendant who responsible for the routine care of the laboratory animals such as feeding, cage cleaning, bedding and cage changing. Similar ratio of 7:3 also documented between workstation of laboratory and animal house in term of type of work area. All the 87 exposed subjects (100%) were handling mouse, while 92.0% exposed to rat, 19.5% exposed to rabbit, 13.8% exposed to cat and 10.5% were exposed to hamster. More than half of the workers were involved in duties with close contact with the laboratory animal allergen, namely: feeding and breeding (71.3%), handled soiled bedding (67.8%), cage cleaning and change of bedding (59.8%) and collecting blood with tissue harvesting (51.7%). In addition, in term of exposure duration, approximately half (50.6%) had 2-5 years of exposure length, followed by exposure of more than 5 years (40.2%); while for the frequency of exposure, 62.1% experienced daily exposure compared to only 37.9% exposed at least once a week. The proportion of exposed subjects who did not comply to the full set of personal protective equipment (PPE) upon contact with laboratory animal allergy was 74.7%. All were completely adhering to the glove worn during various procedure involving laboratory animals, however only 26.4% utilized protective eye glasses, 85.1% wore surgical mask, 23.0% wore respirators, 88.5% wore apron or lab gown and 74.7% wore safety shoes, at all time. The prevalence of atopy among our exposed respondents was one in five (21.8%). Approaching half (47.1%) of the subjects

responded in present study reported that the complete PPE were not provided or not accessible in the work station at all time (Table 4.5).

Table 4.5

Distribution in overall and categories based with Positive LAA symptoms and declined lung function, with their occupational risk factors among the exposed group

Variables	Total		Positive LAA symptoms		Declines lung function	
	n	%	n	%	n	%
Gender						
Male	37	42.5	24	47.1	24	49.0
female	50	57.5	27	52.9	25	51.0
Job description						
Handlers	26	29.9	17	33.3	16	32.7
Users	61	70.1	34	66.7	33	67.3
Type of work area						
Animal house	26	29.9	17	33.3	16	32.7
Laboratory	61	70.1	34	66.7	33	67.3
Type of animals						
Mouse	87	100.0	51	100.0	49	100.0
Rat	80	92.0	47	92.2	46	93.9
Hamster	9	10.5	5	10.0	2	4.1
Rabbit	17	19.5	9	17.6	8	16.3
Cat	12	13.8	8	15.7	8	16.3
Duties/ Nature of work						
Handling stool or urine	41	47.1	21	41.2	25	51.0
Collect blood/ Harvest tissue	45	51.7	20	39.2	20	41.8
Dissection/ Surgical procedure	32	36.8	14	27.5	12	24.5
Handling soiled bedding	59	67.8	35	68.6	37	75.5
Feeding/ Breeding	62	71.3	38	74.5	41	83.7
Change bedding/ Cage cleaning	52	59.8	32	62.7	34	69.4
Handling carcasses	27	31.0	12	23.5	15	30.6
Exposure duration						

Less than 2 years	8	9.2	5	9.8	2	4.1
2-5 years	44	50.6	25	49.0	26	53.1
More than 5 years	35	40.2	21	41.2	21	42.9
Exposure frequency						
Daily	54	62.1	33	64.7	31	63.3
At least once a week	33	37.9	18	35.3	18	36.7
PPE compliance at all time						
Yes	22	25.3	5	9.8	6	12.2
No	65	74.7	46	90.2	43	87.8
Use protective eye glasses at all time						
Yes	23	26.4	6	11.8	6	12.2
No	64	73.6	45	88.2	43	87.8
Wear surgical mask at all time						
Yes	74	85.1	38	74.5	41	83.7
No	13	14.9	13	25.5	8	16.3
Wear respirator at all time						
Yes	20	23.0	5	9.8	6	12.2
No	67	77.0	46	90.2	43	87.8
Wear apron or lab gown at all time						
Yes	77	88.5	41	80.4	42	85.7
No	10	11.5	10	19.6	7	14.3
Wear gloves at all time						
Yes	87	100.0	51	100.0	49	100.0
No	0	0	0	0	0	0
Wear safety shoes at all time						
Yes	65	74.7	31	58.8	34	69.4
No	22	25.3	21	41.2	15	30.6
PPE accessible at all time						
Yes	46	52.9	23	45.1	21	42.9
No	41	47.1	28	54.9	28	57.1
Atopy						
Yes	19	21.8	12	23.5	13	26.5
No	68	78.2	39	76.5	36	73.5

Table 4.5 displayed an illustration of various occupational risk factors based on the categories of positive LAA symptoms as well as abnormal lung function.

Among those exposed workers who presented with at least one positive LAA symptoms, majority were female (52.9%), animal users (66.7%), and working in the laboratory (66.7%). All the animal facilities' workers with positive LAA symptoms experienced history of contact with mouse, with more than half were conducting risky task likes feeding and breeding (74.5%), handling soiled bedding (68.6%) and cage cleaning or change of bedding (62.7%). On the other hand, in term of exposure magnitude, major proportion of those with positive LAA symptoms reported the exposure duration between 2-5 years (49.0%) while 64.3% of the subjects reported the frequency of daily exposure. There was only 6% among this category complied to complete PPE usage during high risk duties, with as high as 88.2% who did not utilize protective glasses and 90.2% did not wore respirators at all time while carrying out their tasks in the research animal facilities. In addition, more than half (54.9%) of the exposed subjects with positive symptoms reported that full set of PPE was not available and accessible at all time. The prevalence of atopy was 23.5%.

On the other hand, for the category of exposed subjects with declined lung function, similarly majority were female (51.0%), animal users (67.3%) and working in laboratory setting. Majority subjects with abnormal function reported handling rodents (100% on mouse while 93.9% on rat), experiencing exposure duration of 2-5 years (53.1%) and reported daily basis of exposure (63.3%). The proportion of workers with

detected decline lung profile who did not comply to the full PPE upon exposure to laboratory animal allergen was high (87.8%). For the respiratory protection, 87.8% reported did not utilized respirator at all time. In addition, one quarter among them (26.5%) had preceding history of atopy.

4.6 The association between LAA symptoms with occupational exposure

Table 4.6 shows the relationship between different LAA symptoms with the occupational exposure to laboratory animal allergen, utilizing chi square analysis in order to compare the proportions between two categorical or qualitative variables in form of cross tabulation tables. The occupational exposure was an important and significant risk factor for the development of various LAA symptoms especially skin, eye, nasal and upper respiratory symptoms. The prevalence of skin symptoms among the exposed group (17.2%) was significantly higher compared to the control group (1.1%, $p < 0.001$). Similar findings were also observed for eye symptoms (18.4% among exposed population compared to zero case among control group, $p < 0.001$) as well as the nasal and upper respiratory symptoms (49.4% among the exposed subjects with 3.4% among the control group, $p < 0.001$). In addition, the incidence of at least one positive LAA symptoms among subjects with occupational exposure was also significant (58.6%) in comparison to the non-exposed controlled subjects (3.4%, $p < 0.001$). Similarly, more than half (56.3%) among the exposed workers had detected significant decline in lung function compared to the control group (3.4%, $p < 0.001$). In

view of the significance of the p- value (< 0.05), therefore the null hypothesis could be rejected. In other words, there were significant differences in the reported skin, eye, nasal and upper respiratory symptoms between the exposed and control group. Moreover, the development of at least one LAA symptoms as well as declined in lung function also showed significant difference between the two independent groups that being tested in present study.

Table 4.6
Prevalence of various LAA symptoms and declined lung function among both exposed and control group

Variables	Exposed group		Control group		Chi square	p value
	n	%	n	%		
Skin symptoms	15	17.2	1	1.1	13.491	<0.001
Eye symptoms	16	18.4	0	0	13.491	<0.001
Nasal and upper respiratory symptoms	43	49.4	3	3.4	47.283	<0.001
Chest Symptoms	0	0	0	0	-	-
At least one positive LAA symptoms	51	58.6	3	3.4	61.867	<0.001
Declined Lung function	49	56.3	3	3.4	58.037	<0.001

4.7 The association between positive LAA symptoms and lung function decline

Among the overall 174 respondents made up of both exposed and controlled subjects, about one in ten (12.1%) with at least one positive LAA symptoms had normal lung values whereas two fifth (19.0%) of those presented with at least one LAA symptoms detected to have abnormal lung function. While for those who did not report any single LAA symptoms, 10.9% were found to have declined lung function upon spirometry examination. These associations were all supported by the significance values of $p < 0.001$ (Table 4.7.1)

Table 4.7.1
The association between positive LAA symptoms and lung function decline in overall subjects

At least one LAA symptoms	lung function					
	Normal		Declined		Chi-square	P value
	n	%	n	%		
Yes	21	12.1	33	19.0	36.436	<0.001
No	101	58.0	19	10.9		

Focusing on the 87 exposed subjects alone , one fifth (20.7%) with at least one positive LAA symptoms had normal lung values whereas almost two fifth (37.9%) of those presented with at least one LAA symptoms detected to have abnormal lung function. While for those who did not report any single LAA symptoms, 18.4% were

found to have declined lung function upon spirometry examination. These associations were all supported by the significance values of $p < 0.001$ (Table 4.7.2)

Table 4.7.2

The association between positive LAA symptoms and lung function decline among the exposed group

At least one LAA symptoms	lung function					
	Normal		Declined		Chi-square	P value
	n	%	n	%		
Yes	18	20.7	33	37.9	3.522	0.049
No	20	23.0	16	18.4		

4.8 The Mean/ Median differences of lung function values between exposed and control group

The mean or median differences between the two independent samples can be evaluated if the tested variables are numerical data with the group variable in form of categorical data. The parametric analysis of independent t-test was employed for Forced Vital Capacity (FVC) in view of the random samples, independent observations, adequate sample size of more than 30, equal population variances of the two groups and most importantly the data was normally distributed in each group. The normality test of Kolmogorov-smirnov showed that p value was significant >0.05 therefore the hypothesis for normality was accepted and the FVC data was normally distributed.

Table 4.8.1
Normality test for FVC

Parameter	group	Kolmogorov-Smirnov ^a		
		Statistic	df	Sig.
FVC	exposed	.121	87	.083
	controlled	.102	87	.077

Table 4.8.2 showed the Independent t-test (parametric test) to evaluate the mean difference of FVC between the exposed and control group. The Levene's Test for equal variances was not assumed due to the significance of p value ($p < 0.001$). As a result, there was significant difference in the mean Forced Vital Capacity (FVC) between the exposed and control group ($p < 0.001$, 95CI: -18.91, -12.07, t statistic= -8.949, df= 135.855). The null hypothesis was rejected.

Table 4.8.2
Independent t-test (parametric test) for FVC between the exposed and control group

Lung Function Value	Exposed group Mean \pm SD	Control group Mean \pm SD	Mean difference \pm SD	95 CI (Lower, Upper)	t Statistic	df	p value
Forced Vital Capacity (FVC)	77.27 \pm 14.06	92.76 \pm 7.95	-15.49 \pm 1.73	-18.91, -12.07	-8.949	135.855	<0.001

On the other hand, the non-parametric analysis of Mann-Whitney U Test was employed for Forced Expiratory Volume at 1 second (FEV1) and the ratio of

FEV1/FVC in view of the assumptions for parametric test were not satisfied. Mann-Whitney U Test is the nonparametric alternative to independent t-test when the dependent variables in both groups were not normally distributed. The normality test of Kolmogorov-smirnov for both FEV1 and the ratio of FEV1/FVC showed that p value was insignificant <0.05 therefore the hypothesis for normality was rejected. The data of FEV1 and the ratio of FEV1/FVC were asymmetrically distributed and hence the median difference between groups will be evaluated rather than mean difference.

Table 4.8.3
Normality Test for FEV1

Parameter	group	Kolmogorov-Smirnov ^a		
		Statistic	df	Sig.
FEV1	exposed	.121	87	.003
	controlled	.102	87	.000

Table 4.8.4
Normality Test for FEV1/FVC

Parameter	group	Kolmogorov-Smirnov ^a		
		Statistic	df	Sig.
FEV1/FV	exposed	.112	87	.009
C	controlled	.138	87	.000

Table 4.8.5 showed the non-parametric test of Mann Whitney U test for FEV1 value and the ratio of FEV1/FVC for both the exposed and control group. There was significant median difference of the FEV1 value ($U=1147$, $p<0.001$) and the FEV1/FVC ratio ($U=2592$, $p<0.001$) between the two independent groups. The null hypothesis being rejected.

Table 4.8.5

Mann Whitney U test (Non-Parametric test) for FEV1 and FEV1/FVC ratio for both the exposed and control group

Lung Function Value	Mean rank Exposed group	Mean rank Control group	Mann Whitney U statistic	p value
FEV1	57.18	117.82	1147.0	<0.001
FEV1/FVC	73.79	101.21	2592.0	<0.001

4.9 Associated risk factors for LAA among the exposed subjects

Prior to the employment of multiple logistic regressions to examine the association between various occupational and environmental risk Factors with the development of LAA among the exposed population, the Hosmer-Lemeshow test was used to test the fitness of model. In the Pearson Chi Square test in the Goodness-of fit, $p > 0.05$ indicating that the null hypothesis of model fitness cannot be rejected therefore the overall model for logistic regression was fit.

Multiple logistic regression (Table 4.9) revealed that male workers (AOR=0.054, 95% CI : 0.003-0.969, $p < 0.05$), workers who did not compliance to full Personal Protective Equipment at all time during contact with laboratory animal (AOR=7.619, 95% CI : 1.568-37.009, $p < 0.05$), those with positive history of atopy (AOR=0.056 , 95% CI : 0.005-0.702, $p < 0.05$) and also being current or ex-smoker (AOR=0.063 , 95% CI : 0.004-0.939, $p < 0.05$) were more likely to develop LAA , evidenced by the report of at least one positive LAA symptoms or the declined of lung function or both, compared

to their respective references counterparts. However, other risk factors such as educational level, job description, type of work area, exposure duration, exposure frequency, PPE accessibility and home pets were found to have no association with the development of LAA.

Table 4.9

Association between occupational and environmental risk factors with the development of LAA among the exposed subjects

Variables	LAA (positive LAA symptoms or declined lung function or both)		
	Adjusted Odd Ratio (AOR)	95 CI	p value
Gender			
Male	0.054	0.003-0.969	0.048
Female	Ref		
Education level			
Secondary	0.592	0.029-11.878	0.732
Tertiary	Ref		
Job description			
Handlers	2.241	0.531-9.459	0.251
Users	Ref		
Type of work area			
Animal house	0.638	0.073-5.592	0.685
Laboratory	Ref		
Exposure duration			
< 2 years	1.669	0.175-15.917	0.656
2-5 years	3.273	0.693-15.465	0.135
>5 years	Ref		
Exposure frequency			
Daily	1.028	0.279-3.789	0.967
At least a week	Ref		
Handling more than one type animals			
Yes	4.07	1.236	
No	Ref		
PPE compliance			
Yes	Ref		

No	7.619	1.568-37.009	0.012
PPE Accessibility			
Yes	Ref		
No	6.287	0.811-48.714	0.078
Atopy			
Yes	0.056	0.005-0.702	0.025
No	Ref		
Smoking Status			
Non smoker	Ref		
Current and Ex-smoker	0.063	0.004-0.939	0.045
Owns Home pet			
Yes	2.818	0.444-17.900	0.272
No	Ref		

4.10 Hypothesis testing

There were seven main hypotheses being generated in the study.

H1a: The exposed group is significantly more likely to develop Laboratory Animal Allergy (LAA) symptoms compared to the controlled group, was supported (Table 4.6). The prevalence of reported skin, eye, nasal and upper respiratory symptoms among the exposed group were significantly higher compared to the control group ($p < 0.001$). In addition, the incidence of at least one reported positive LAA symptoms among the exposed subjects were also significant in comparison to the non-exposed controlled subjects ($p < 0.001$).

H1b: The exposed group is significantly more likely to have declined lung function compared to the controlled group, was supported (Table 4.6). The incidence rate of

declined lung function among the exposed subjects was significantly higher compared to the non-exposed controlled subjects ($p < 0.001$). In addition, while examining the numerical data of lung function values in between two groups, independent t-test showed significant difference in the mean Forced Vital Capacity (FVC) between the exposed and control group ($p < 0.001$, 95CI: -18.91, -12.07, t statistic= -8.949, df= 135.855). On the other hand, for abnormally distributed data, Mann Whitney U Test had also showed significant median difference of the FEV1 value ($U = 1147$, $p < 0.001$) and the FEV1/ FVC ratio ($U = 2592$, $p < 0.001$) between the two independent groups.

H2: There is significant association between Laboratory Animal Allergy (LAA) symptoms and the declined lung function was supported. In overall subjects, approaching three-fifth of those presented with at least one LAA symptoms detected to have abnormal lung function (Table 4.7.1); while focusing on the exposed group solely, similarly almost three fifth of those presented with at least one LAA symptoms detected to have abnormal lung function (Table 4.7.2). These associations were all supported by the significance values of $p < 0.001$.

H3: Among the exposed group, workers with higher magnitude of exposure (duration and frequency) are more likely to develop Laboratory Animal Allergy (LAA) compared to those with lower magnitude of exposure., was not supported (Table 4.9). Multiple Logistic Regression analysis showed insignificant association between both the exposure duration and exposure with the LAA development ($p > 0.05$).

H4: Among the exposed group, animal handlers are more likely to develop Laboratory Animal Allergy (LAA) compared to the animal users was not supported (Table 4.9). Multiple Logistic Regression analysis showed insignificant association between job description either the animal handlers or animal users with the LAA development ($p>0.05$).

H5: Among the exposed group, workers working in animal room are more likely to develop Laboratory Animal Allergy (LAA) compared to those who works in the laboratory, was not supported (Table 4.9). Multiple Logistic Regression analysis showed insignificant association between type of work area either in the animal house or laboratory with the LAA development ($p>0.05$).

H6: Among the exposed group, workers comply to full PPE are more likely to develop Laboratory Animal Allergy (LAA) compared to those who do not comply, was supported (Table 4.9). Multiple Logistic Regression analysis showed significant association between the PPE compliance with the LAA development ($p<0.05$).

H7: Among the exposed group, workers with atopy are more likely to develop Laboratory Animal Allergy (LAA) compared to non-atopic, was supported (Table 4.9). Multiple Logistic Regression analysis showed significant association between the underlying atopy with the LAA development ($p<0.05$).

H8: Among the exposed group, workers reported positive smoking status are more likely to develop Laboratory Animal Allergy (LAA) compared to non-smokers, was supported (Table 4.9). Multiple Logistic Regression analysis showed significant association between smoking status with the LAA development ($p < 0.05$).

H9: Among the exposed group, workers who own home pets are more likely to develop Laboratory Animal Allergy (LAA) compared to those without home pets, was not supported (Table 4.9). Multiple Logistic Regression analysis showed insignificant association between the owning of home pets with the LAA development ($p > 0.05$).



Table 4.10
The results of hypotheses testing

Hypothesis	Result
H1a: The exposed group is significantly more likely to develop Laboratory Animal Allergy (LAA) symptoms compared to the controlled group.	Supported
H1b: The exposed group is significantly more likely to have declined lung function compared to the controlled group.	Supported
H2: There is significant association between Laboratory Animal Allergy (LAA) symptoms and the declined lung function.	Supported
H3: Among the exposed group, there is a significant association between the magnitude of exposure (duration and frequency) with the development of Laboratory Animal Allergy (LAA) .	Not supported
H4: Among the exposed group, there is a significant association between the job descriptions with the development of Laboratory Animal Allergy (LAA).	Not supported
H5: Among the exposed group, there is a significant association between the type of work area with the development of Laboratory Animal Allergy (LAA).	Not supported
H6: Among the exposed group, there is a significant association between the compliance of personal protective equipment (PPE) usage with the development of Laboratory Animal Allergy (LAA) .	Supported
H7: Among the exposed group, there is a significant association between history of atopy with the development of Laboratory Animal Allergy (LAA).	Supported
H8: Among the exposed group, being a smoker is significantly associated with the development of Laboratory Animal Allergy (LAA).	Supported
H9: Among the exposed group, own of home pets is significantly associated with the development of Laboratory Animal Allergy (LAA).	Not supported

4.11 Summary

This chapter presented the findings following data collection and data analysis. The statistical analysis had employed five main analytic methods namely descriptive and frequency analysis, cross tabulation or chi square test, independent t-test, Mann Whitney U test and Multiple Logistic Regression. In overall, six out of a total of ten hypotheses were supported in present study.



CHAPTER FIVE

DISCUSSION AND RECOMMENDATION

5.1 Introduction

This chapter elaborates and explained in details besides supported by literatures all the findings obtained in present study. The results of the research will be discussed especially on the aspect of the prevalence of LAA, the incidence of declined lung function among the workers exposed to laboratory animal allergen as well as the identification of its associated risk factors. Following discussion, the implications of the overall study will be identified, theoretically and practically in order to improve the occupational safety, health and wellness among the exposed population. In addition, the limitations encountered throughout the study will be highlighted, along with the suggestions for future improvement.

5.2 Prevalence of Laboratory Animal Allergy (LAA)

The prevalence of positive LAA symptoms among the exposed population in present study was 58.6%. There was zero case for work-related asthma. Our proportion was slightly higher compared to those documented in the literature across different countries. Multitude cross-sectional study had been constantly reported that the prevalence of LAA development ranging from 10% to 46% (Aoyama et al.,1992) ,while some estimated the prevalence of 10%- 23% (Lutsky, & Neuman, 1975;

Hollander, Doekes, & Heederik, 1997), and over 40% of LAA incidence had been reported (Venables et al., 1988). The National Institute for Occupational Safety and Health Boston estimated the prevalence of 33% of laboratory animal handlers develop allergy symptoms. The discrepancy in the prevalence might be due to the dissimilarities in workplace setting, laboratory routines and nature of exposure. This could also be explained by the differences in the diagnosing criteria applied in different study although many studies estimated incidence of LAA utilizing self-reported symptoms. In addition, the animal species is an important determinant for the development of LAA. Rodents appeared to be the most allergenic species and in present study 100% of the exposed population was reported handling with mouse. The previous studies were cross-sectional in nature which deals with the survivors' population. If an entire population was traced the true prevalence might be as high as 50% (Nieuwenhuijsen et al., 2003). Rodents (mice and rats) are among the most abundantly used laboratory animals in medical research therefore are generating the most common occupational allergic disorder clinically (Bush, Wood, & Eggleston, 1998). Current study revealed that 100% of all the exposed subjects reported being handled with laboratory mouse, while as high as 92.2% had contact with laboratory rat. These rodents persistently shed allergens through body secretions and deposited around the working environment. The difference in the LAA prevalence could be also due to the variation in the methodology in different study, the different criteria being used to recruit subjects and also different criteria for the LAA definition.

In line with previous studies, this study had reported a more prevalent of LAA symptoms involving nasal and upper respiratory tract compared to skin and eye symptoms. 49.4% from the exposed group in overall complaint of nose and upper airway discomfort, and this proportion made up of 84.3% among the symptomatic exposed population. Respiratory allergy had been reported very much common compared to skin and eye allergies (Seward, 2001). The National Institute for Occupational Safety and Health Boston had documented the most usual manifestations of stuffy or runny nose. The estimation of 70-80% of symptomatic workers were reported to have upper airway symptoms (Aoyama et al., 1992; Bush, Wood, & Eggleston, 1998; Elliott, Heederik, Marshall, Peden & Loomis, 2005). Majority of the disease typically began with rhinitis and subsequently progress into occupational asthma in a year or two. This indicated that lung function test is important in detecting lung impairment even in those exposed population who did not display LAA symptoms.

There were no chest or asthmatic symptoms being reported in current study. However, approximately 10% of the animal handlers will eventually develop work-related asthma in later stage, and those who develop LAA are at higher risk of developing occupational asthma (Bush & Stave, 2003; Gordon & Preece, 2003; Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). The absence of asthmatic case in present study still could be due to job transfer by those with developed chest symptoms which resulted in smaller numbers being surveyed in this study. Therefore

the effective preventive measures must be implemented in order to prevent the symptomatic workers from progressing into asthmatic event in the future.

On the other hand, Ferraz et al. (2013) reported the occupational sensitization prevalence of 16% and 3 % between animals' handlers and non-handlers respectively in one study exploring the correlation between laboratory animals with respiratory allergies. The findings reported among the non-animal handler by Ferraz et al. (2013) was similar with present study which documented 3.4% of LAA incidence among workers without direct occupational exposure to laboratory animal allergen. It was possible that this minority of non-animal handlers might develop allergic symptoms from other unmeasured allergens or even the environmental irritants such as dust mites and cleaning agents, or even non occupational exposure to household pets. Allergies to cats and dogs had been identified as an essential risk factor for LAA (Hollander, Doekes, & Heederik, 1997).

5.3 Occupational influence on the development of LAA symptoms and declined lung function

The occupational exposure plays an important and significant role in the development of various LAA symptoms especially skin, eye, nasal and upper respiratory symptoms. The prevalence of skin, eye , nasal and respiratory symptoms in this study were significantly higher compared to the control group, so did the prevalence of at least

one positive LAA symptoms as well as lung function decline, both were significantly more prevalent among subjects with occupational exposure.

Workers exposed to laboratory animal allergen had a clear source of exposure. Research laboratory had been identified as a risky environment for the allergies development among the users (Taylor, Longbottom, & Pepys, 1977; Harries, & Cromwell, 1982). The laboratory animals were persistently shedding allergens in their body waste, urine, saliva, dander, hair as well as skin desquamation. As a result, these allergens are small size particle that deposit on the laboratory equipment or retained in the air hence easily breathe in. Once workers developed sensitization towards specific allergens, continued exposure may lead to progressive and chronic lung function loss (Paggiaro, 1994; Venables, & Chan-Yeung, 1997). In line with these, several studies among laboratory animal workers were also demonstrated that exposure and sensitization to laboratory animal allergens was associated with lung function decline (Renstrom, Malmberg, Larsson, Larsson, & Sundblad, 1995 ; Fuortes, 1997).

The expose-response relation existed between the occupational exposure and the development of LAA. Previous studies reported that chest and skin symptoms were evidently associated with high intensity of exposure to rat urinary allergen (Cullinan et al., 1999 ; Nieuwenhuijsen et al., 2003). However, there were some inconsistency being reported between the magnitude of exposure and the LAA development: some literature expressed a greater LAA cases among workers with aggressive exposure

such as animal handlers (cage cleaners) (Cullinan et al.,1999) while some reported a more prevalent of LAA among workers with low level but prolonged exposure such as the animal users (laboratory technicians and scientist) (Aoyama et al.,1992). The present study revealed that among the exposed group, majority of the positive cases for LAA symptoms (66.7%) and lung function decline (67.3%) were reported among the animal users compare to handlers. Besides the nature of work which required prolonged contact with laboratory animal during experiments among the animal users, another plausible reason was the total sample from animal users were higher than animal handlers with the ratio of 3:1 in current study. Besides, 100% of those in contact with mouse and 92.2% of whom handling laboratory rat were reported positive LAA symptoms. The rodents including mice and rat are the most widely used species in medical laboratory research worldwide (Bush, Wood, & Eggleston, 1998), therefore were recognized as the laboratory animal that posted most incidence of LAA.

LAA clearly occurred among the animal handlers. The laboratory animals which have allergenic protein were being used abundantly (Cullinan et al.,1999 ; Nieuwenhuijsen et al., 2003). The lung function might decline more rapidly in those workers exposed to allergens in their work environment, particular in people with occupational respiratory diseases (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003).

5.4 Association between the self-reported LAA and declined lung function

LAA was common in commercial, governmental as well as academic institutions which perform experimental research utilizing laboratory animal. One fifth (20.7%) among the exposed population reported positive LAA symptoms however confirmed normal lung function. The symptoms reported although mild and without significant chest involvement, however might lead to chronic impairment thus reduced the workers' wellbeing in long term as literature had reported the simple LAA symptoms that progressed into occupational asthma (Bush & Stave, 2003; Gordon & Preece, 2003; Portengen, Hollander, Doekes, De Meer, & Heederik, 2003).

A significant proportion of exposed subjects who presented with at least one LAA symptoms at the same time detected decline in lung function in present study. Workers who experienced LAA during or shortly after working with laboratory animals tended to have significant airflow obstruction compared to those without allergic symptoms. In homogenous with this, subjects who reported allergic symptoms typically nasal and respiratory symptoms shortly after contact with laboratory animals were found to have lower lung function value in FEV₁, while compared to those who did not display any symptoms (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Moreover, a strong positive relationship was found in between the presence of LAA symptoms and lung function impairment especially in workers exposed more than four years.

Lung function examination as the changes of lung function had been reported to be directly proportional to the extent of exposure to laboratory animal allergen (Enarson, & Yeung, 1985). Besides, significant lung function decline was also found among laboratory animal workers with less than four years occupational contact ,who were sensitized with continuous exposure (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003 ; Gordon, & Preece, 2003). The exhibition of significant obstructive pattern from the lung function test typically indicates the possibility of occupational asthma.

As high as 18.4% of the asymptomatic exposed subjects however accidentally discovered decline in lung function during spirometry. Clinically relevant airway obstruction can be the impact of continuous exposure to laboratory animal allergen over few years. Nevertheless, lung impairment probably occurred in the absence of prominent LAA symptoms (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Therefore, lung function assessment is crucial not only to detect the degree of lung impairment (Bush, 2001), but also as a confirmatory clinical evaluation if laboratory animal allergen induced asthma is suspected. Practically spirometry should be performed among workers complaint of chest symptoms likes cough, shortness of breath, wheezing and chest tightness. However, it was also found to be advantageous in detecting subclinical asthma when workers only presented with upper airway symptoms such as nasal congestion, runny nose, itchy nose and sneezing (Malo, & Chan-Yeung, 2001).

The present study showed significant association of the LAA symptoms with abnormal lung function among the exposed workers. The assessment of the association between the LAA symptoms and impaired lung function is imperative as sensitization had been reported in the literatures which demonstrated the progression from mild rhinitis and conjunctivitis into occupational asthma in later stage (Eggleston & Wood, 1992; Bush & Stave, 2003; Solé, Camelo-Nunes, Wandalsen, Rosário & Sarinho, 2011).

5.5 Difference in the lung function values between animal handlers and the control group

Lung function test was performed at every Thursday and Friday in order to allow the possible indicator of work-week effect and therefore the results obtained was considered reliable. While examining the difference of lung function values between the exposed and control group, the mean forced vital capacity (FVC), as well as the median forced expiratory volume at one second (FEV1) and the ratio of FEV1/FVC among the control subjects were all documented a significantly higher values compared to their counterpart in the exposed group. Abnormally low values signify certain level of lung impairment, could be obstructive or restrictive. The reduction in FVC was paralleled by similar drop in FEV1 which highly suggested of obstructive lung disorder. These were in congruent with the literatures which consistently reported the accelerated lung function decline among the laboratory animal workers

(Sjöstedt, Willers, & Ørbæk, 1993; Renstrom, Malmberg, Larsson, Larsson, & Sundblad, 1995; Fuortes et al., 1997). The lung function impairment somehow can also occur without prominent clinical symptoms of LAA. The exposure to laboratory animal itself especially among those sensitized workers had been recognized as an important risk factor for longitudinal lung function decline while examined cohortly (Renstrom, Malmberg, Larsson, Larsson & Sundblad, 1995 ; Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Therefore present study is recommended to be carried on further in order to follow up all subjects with prominent LAA symptoms or decline in lung function, according to cohort study design. The lung function findings obtained from present study was reliable due to the work-week effect where the spirometry was performed on every Thursday or Friday.

The exposure to laboratory animal allergens was a significant risk factor for the development of airflow obstruction in the respiratory system ((Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). In line with this, previous study even concluded that laboratory animal workers were at high risk of developing clinically relevant airway obstruction (Buist & Vollmer, 1988). This mechanism could be best explained by the continued exposure to animal allergen which lead to chronic low level inflammation in the body. As a result, workers became sensitized with chronic airflow limitation and finally detected declined lung function clinically (Howarth et al., 1991; Djukanovic et al., 1992; Shaver et al., 1995).

The remarkable findings on the difference of lung values between the exposed and control group indicated that preventive program is mandatory. All sensitized workers

were now being identified, thus they should be monitored closely to limit the negative health consequences as well as to improve the prognosis. Multiple countries had incorporated the preventive programs into the legal requirements. In term of policy implications, the sensitized asymptomatic workers with abnormal lung function should be considered for exposure removal (Portengen, Hollander, Doekes, De Meer, & Heederik, 2003). Nevertheless, it must be taken into consideration that some independent variables are known predictors for decline in respiratory function such as gender, age and smoking status.

5.6 Associated risk factors for LAA

Multiple Logistic analysis had been employed to evaluate the risk factors associated with LAA symptoms and lung function decline and found that being male, those not compliance to full PEE at all time, workers with preexisting atopy as well as the smoking exposed individuals were more likely to develop LAA symptoms or detected decline lung function or both.

Some individuals have coexisting allergic reactions (atopy) towards substances outside their work environment which might increase their risk of developing LAA. In line with the present findings, earlier analyses had documented a strong association between atopy and sensitization to laboratory animal. Similar observation being reported for lung function decline (Portengen, Hollander, Doekes, De Meer &

Heederik ,2003). Atopy was known to have strong association with chest symptoms. As reported in present study, 26.5% of the exposed subjects who had underlying atopy and detected decline lung profile. Ample studies reported that individuals with atopy background have tendency to develop immediate type immunology responses upon exposure to aeroallergens in the environment. It was also a well-documented risk factor for the LAA development (Jeal, Jones & Cullinan, 2010). In addition, employees with atopy were found to be more likely to develop occupational asthma secondary to allergen exposure at work, and even more likely to be involved in sickness absenteeism or job transfer secondary to the manifestation of LAA symptoms (Kruize et al.,1997). Atopy is the tendency to develop allergic symptoms which is inherited and closely associated with positive family history. It had been demonstrated that atopic workers have higher relative risk of 4.2 times to develop LAA compared to the non-atopic counterparts. The mean latency period for LAA among the atopics were significantly shorter which result in the onset of symptoms following animal allergen exposure probably shorter (Kruize et al.,1997). To support this explanation, Bland and colleagues (1986) had also reported in their earlier study that 51.2% of the LAA cases were having history of atopy compared to 20.8% among controls (Bland, Levine, Wilson, Fox & Rivera, 1986). The mechanism proposed was due to a stronger exposure response relationship between atopy and LAA development as postulated in several studies therefore making it an important risk factor among the exposed workers (Cullinan et al.,1994; Jeal, Jones & Cullinan, 2010). The genetic predisposition in atopics promoted formation of IgE which could enhance the allergenic responses in human body (Bush & Stave,2003; Jones, 2015). As a result,

altogether these findings reflected that exposure above specific threshold for the atopics and even at the lowest exposure level, might increase the risk of LAA up to threefold (Heederik et al.,1999). Therefore, pre-employment screening to rule out atopy for individual susceptibility is of paramount importance as it is helpful in alerting the risky group to take extra protective measures upon contact with laboratory animal (Botham, Lamb, Teasdale, Bonner & Tomenson, 1995; Bush, Wood, & Eggleston, 1998). Besides it served as clear implications for the organizational policy especially in employment recruitment by practically providing skin prick test.

Smoking had been found to be a risk factor in LAA development as presented in current study which was supported by previous researches (Das et al.,1992; Fuortes et al.,1996; Cullinan et al.,1999). On the other hand, Fuortes and colleagues (1997) had also reported that individuals with positive smoking status were more likely to have significantly greater decline in lung function. The impact of tobacco smoking would increase the risk of LAA in addition to exposure to animal allergen due to an elevation of IgE (Bush & Stave, 2003; Jones, 2015) and may progress LAA into occupational asthma (Jones, 2015). Besides, it was postulated that the effect of smoking may shorten the latent phase before LAA developed (Venables et al.,1988). However the role of tobacco smoking as a risk factor for LAA warrants future prospective studies. At the same time, workplace should implement measures in the smoking prevention and discouragement among workers in order to minimize the adverse health impacts.

Exposed subjects who were reported not compliance to full PPE upon contact with animal allergen were more likely to report LAA symptoms or detected decline lung function. This present study revealed a huge proportion of 74.7% of the animal facilities' workers who did not comply to the full PPE (goggles, gloves, lab gown, respirator and safety shoes) during animal contact, and from this proportion, 90.2% were complaint of positive LAA symptoms while 87.8% detected abnormal lung profile. These findings mandated the use of full PPE especially the respiratory protection. One US survey involved 198 animal facilities discovered a wide variation in the utilization of PPE (Stave & Darcey, 2012). The task force of European Respiratory Society announced that usage of PPE, although may not provide complete protection somehow lead to improvement in respiratory symptoms (Vandenplas, Dressel, Nowak & Jamart, 2012). PPE had been introduced as a component of the laboratory animal allergen exposure reduction program worldwide (Jones, 2015). In addition, employees who utilize face mask since their very first employment were reported to have lower prevalence of LAA development especially the respiratory sensitization (Jones, Schofield, Jeal & Cullinan, 2013). The PPE utilization not only reduces exposure to animal allergen but also protects users from infectious agents. The surgical or face masks although provides certain degree of protection somehow do not function as the respirator which provides a higher protection level against those laboratory animal allergen (Seward, 2001). Unfortunately, there was only one quarter of the exposed subjects in present study utilized respirator at all time while almost half (47.1%) reported the full PPE not accessible at all time. The risk of occupational contact with animal allergen often misjudged in which PPE only will be utilized once

symptoms appeared and experienced by the workers (Ferraz ,2013). Nevertheless, previous study discovered a LAA symptoms reduction by 58% upon utilization of full PPE (Bland, Levine, Wilson, Fox & Rivera, 1986). On the other hand, the introduction of mandatory use of PPE in order to reduce exposure among the workers exposed to animal allergen successfully reduced the LAA incidence from 37% to 12% within 5 years (Botham, Davies & Teasdale, 1987). The organization should take the responsibility in providing complete and adequate PPE to all employees in order to maintain their safety, health and welfare as written under section (15) Occupational Safety and Health Act 1994. The employers must ideally implement the respiratory protection program involving the fit test, medical approval before use as well as the quality control. There are no clear regulatory standards on the exposure level to animal allergen and the permissible exposure limit to animal allergens has not been developed. Therefore the respirator selection must base on work activities, intensity of exposure and the assessment on work environment (Seward,2001). Typically face masks approved by National Institute of Occupational Safety and Health had been shown to remove up to 98% of the allergen from rodents' urine deposited in the air (Sakaguchi et al.,1990). On the other hand, other PPE such as gloves, gown and protective clothing are crucial to keep the allergens away from the skin however workers must make sure they remove these garments before going home at the end of work shift to avoid carrying home that occupational allergen.

Present study did not reveal association between the development of LAA and job description, type of work area, duration and frequency of exposure, most probably due

to variance in level, potency, pattern and nature of exposure among the exposed workers (Elliott, Heederik, Marshall, Peden & Loomis, 2005). In contrast to the present findings, studies had reported a higher rate of LAA among the animal handlers (animal care takers) compared to the animal users (scientist and lab technicians) and the risk increased with an increased exposure in term of hours per week as well as tasks involving working with many animals at one time (Elliott, Heederik, Marshall, Peden & Loomis, 2005). The nature of animal contacts such as numerous types of contact procedures, number of animals in contact per one time was crucial and served as an indicator to predict the development of LAA. Furthermore, the present study was relatively small to draw any conclusion towards possible relationship between these occupational risk factors with the LAA development.

Unfortunately, although we have included all workers with positive occupational contact with laboratory animal, the subgroups under each independent variable were too small to allow meaningful analysis. This study aimed to be expanded into more institute or workplace where exposure to laboratory animal is significant in order to obtain a larger sample size for a more powerful study.

5.7 LAA Prevention Program

The prevention of LAA is very much depending on the control of allergenic substances in the work environment (Seward, 2001). Exposure avoidance is always the best way to prevent LAA. Primary control techniques includes exposure reduction by the implementation of control measures (reduce the use of laboratory animal , environmental control in the animal facilities and limiting the number of workers with access into the animal facilities); while secondary control tool covers medical surveillance program for early identification of the LAA.

The National Institutes of Health had recommended a few mandatory measures to be incorporated into an effective Laboratory Animal Allergy Prevention Program (LAAPP) (Nancy Figler DVM, 2004). Firstly, the engineering control. The ventilation especially local exhaust ventilation must be provided suitable for its tasks: the biological safety cabinets or bench equipped with local ventilation, usage of filter top cages and ventilated animal racks, installation of the High Efficiency Particulate Air (HEPA) filtration, besides giving special attention to cage dumping or cleaning.

Secondly, the administrative control which covers the design of the animal facility in order to minimize animal transfer as well as ensure regular housekeeping with wet method but not sweeping to reduce the level of inhalable animal dust. In addition, training, supervision and education on personal hygiene, the usage of PPE not

forgotten the awareness on relevant allergic signs and symptoms are equally important.

Thirdly, The medical evaluation and occupational health program where all risky employees should be provided a periodical medical evaluation. Furthermore, they must be urged to report or notify any of the LAA symptoms immediately. The pre-placement medical examination is valuable for the employees to recognize their personal health risk related to the contact with laboratory animal. Counseling and education shall be provided by the physician to teach employees about the sign and symptoms of LAA. Moreover, pre placement screening is important to establish a baseline so that any future changes in health status can be measured and monitored (Seward,2001).

Fourthly, the personal protective equipment (PPE) recommended for the contact with laboratory animal are nitrile glove, disposable lab gown, goggle, face mask and safety shoes. The use of dust masks is suggested whenever the soiled bedding or the animals are being handled, while N95 respirators are highly recommended for allergic employees.

Finally, the evaluation of the LAA Prevention Program is always important that regular review should be carried out to access its effectiveness in successfully preventing incidence of LAA and work related asthma among the exposed population.

5.8 Implications

This study focuses on the Laboratory Animal Allergy (LAA) symptoms and the lung function decline among the workers exposed to occupational animal allergen. It also identified various associated occupational and environmental risk factors including, duration and frequency of exposure, PPE compliance, type of work area ,job description , history of atopy, smoking status and . Therefore, the important implications in term of theoretically and practically will be declared as following:

5.8.1 Theoretical implications

Workers with close and regular contact with the furred laboratory animals typically develop allergic reactions and sensitivity manifestations. As a result, Laboratory Animal Allergy (LAA) represent a major occupational disease mainly targeting on the exposed population including animal caretakers, laboratory technicians, veterinarian and scientists where their work significantly require such a high risk exposure. The work activities associated with high level of animal allergens likes cage cleaning are more likely to cause respiratory or airway allergic reactions (Bush, Wood, & Eggleston, 1998).

Hence, this study aimed to expand the theory on LAA among the exposed population besides provided the body of knowledge on the associated risk factors of LAA. On the other hand, the empirical evidence of the patterns of LAA had been generated via

present study. There was limited research being conducted among the workers exposed to laboratory animals worldwide while majority of the studies were carried out decades ago. Therefore, the empirical gap existed between the findings generated in the past and the most recent status of LAA among the risky group was demonstrated in this study.

5.8.2 Practical implications

Practically, this study holds a few implications to DOSH, the Ministry of Health (MOH), employers as well as the affected employees.

First of all, this study reported the preliminary data on the incidence of LAA among workers in research animal facilities in Institute for Medical Research (IMR), Malaysia and the study can be further expanded by the regulatory body or MOH to other research institutions or even pharmaceutical industries which require workers to expose to laboratory animals. Following that, further interventions can be implemented in order to improve the safety and health status of this specific exposed population at the same time to strengthen the occupational safety and health system in Malaysia. Multitude occupational safety and health researches had been given focus on huge industries which comprised of substantial proportion of workers such as the manufacturing sector, construction sector, hospitality as well as oil and gas sector however none of the research being conducted among workers exposed to laboratory animal allergen being conducted in Malaysia. This risky working population, although only exists in small proportion in our country, however should not be marginalized in

view of the excellent occupational safety and health service should cover all workers from different working environment.

On the other hand, for the employer and top management, this clinical survey is important in determining the prevalence and incidence of LAA among the exposed workers in the research animal facility, together with its associated occupational risk factors. This finding will provide a guide on the design of the comprehensive occupational health program. The LAA prevention should be the primary goal of a successful safety and health program in the workplace handling with research animals. The program can be accomplished by the modification in facility design, exposure reduction, education and training among the risky employees.

Early recognition of LAA symptoms will facilitate interventional program with the ultimate aim to avoid or minimize the chronic health disability. Early detection ensures early treatment and rehabilitation with an excellent prognosis. Besides, the active clinical surveillance program will definitely play a crucial role in improving health status of the employees working with laboratory animals (Bush, Wood, & Eggleston, 1998). LAA is a preventable occupational hazard. One study revealed the LAA incidence of 10.3% among workers exposed to laboratory animals in a pharmaceutical company. Nevertheless, the prevalence was successfully reduced to zero following a comprehensive occupational safety and health program consisted of a number of environmental control measures in order to reduce the allergen exposure (Fisher, Saunders, Murray, & Stave, 1998). Therefore, knowing the existing

prevalence of LAA together with the associated risk factors is of paramount importance for the establishment of future occupational safety and health prevention program.

Identification of the individuals who are at risk is an essential goal of the screening program. On the other hand, it can also help identify the personnel with preexisting allergies or asthma unrelated to occupational exposure as known as atopy. This assessment, although cannot be legally utilized as the criteria to preclude workers, however holds an imperative value in task assignment which substantially minimize the exposure level towards animal allergen. The employees with predisposing sensitization to laboratory animal should have given the low-risk assignments. In addition, this study serves as a baseline data to identify sensitization in workers who might later develop LAA symptoms. Apparently, individuals with known sensitivity to laboratory animal must avoid repetitive and chronic exposure besides closely monitored for the development of chest symptoms to prevent occupational asthma. Present study hence holds an additional valuable point for the prevention of permanent disability following chronic negative health impacts. The surveillance program holds the value of examining health status of the exposed workers besides allows the utilization of population analysis to improve the OSH program targeting on the exposed group (Seward, 2001).

The clinical surveillance, if run alongside a well-constructed occupational hygiene survey, may offer an opinion on the development of hygiene standards in term of

permissible exposure limit to indoor animal allergen. While on the institutional basis, the findings discovered in present study will help elaborate the institute OSH policy, laboratory work system as well as training and educational approaches. The results also support the necessity of future research effort to explore the important roles of each preventive measure in specific besides to conduct cost-beneficial analysis for the prevention of laboratory animal allergens.

There is currently no standard specifies occupational exposure limit of laboratory animal allergen under OSHA. Nevertheless, the early recognition of occupational and environmental risk factors has urged the implementation of control measures in the laboratory settings hence lead to a decline in the prevalence of LAA as well as work related asthma as reflected in previous study (Folletti, Forcina, Marabini, Bussetti, & Siracusa, 2008)

The knowledge on prevalence and incidence of LAA will determine the effectiveness of the LAA prevention program. Active medical surveillance is always favorable in identifying cases than passive surveillance which fully depending on workers' reporting. Baseline health assessment and periodic clinical survey is helpful as evidently recommended by 109 studies (Nicholson, Mayho, Roomes, Swann, & Blackburn, 2010), utilizing the published prototype questionnaire (Seward, 2001; Bush & Stave, 2003). Hence, the data from current study confirmed the necessity of periodic medical surveillance program for all workers in contact with laboratory

animal allergen, and the cost of the program definitely lower compared to the cost of treatment for occupational asthma or other associated disability.

5.9 Recommendations

Several limitations had been encountered in this study. Firstly, the cross-sectional study design limited the causal-effect relationship therefore restricted the causal inferences to be made about the research findings. Therefore, it would be practical to follow up with all exposed subjects in prospective cohort as the re-examination in the future might be useful to understand the relationship between exposure and health impacts. Secondly, the Laboratory Animal Allergy (LAA) symptoms together with the occupational and environmental exposure history were all based on self-report, which might be affected by reporting bias. Although the LAA questionnaire was specifically designed to avoid leading questions, somehow it was subjective when came across the subjects' correlation between the LAA symptoms and occupational exposure. The memory bias was unavoidable. Besides, another limitation was the "worker's health effects" which may underestimate the true prevalence of LAA secondary to the earlier abandonment of the work activity or job position by those symptomatic subjects. Hence, greater asymptomatic subjects would be remaining in the exposed group thus reducing the true LAA prevalence. A prospective research is highly recommended in the future to prevent such a bias. The other limitation of our study was that although the clinical diagnostic test of spirometry had been employed to detect underlying lung impairment, however the confirmatory immunological test

such as skin prick test was not performed due to budget constraint. Being an invasive procedure, skin prick test however holds the values to confirm the types of allergen that causes positive skin reaction. Furthermore, the assessment on work environment allergen measurements can also be conducted in future studies in order to allow the quantification of risk estimates.

Despite the mentioned limitations, the current study provides a valuable insight into the prevalence and factors associated with the development of Laboratory Animal Allergy among the workers exposed to laboratory animal allergy mainly in the research institute. The sample size was small however the study managed to recruit all exposed subjects with a full response rate. Similar study shall in the future expand to the exposed workers in other research institutions and even the pharmaceutical industries in Malaysia which requires their workers to expose to experimental animals.

Current study had also highlighted the fact that specific workplace-based research allows exposure measurements compared to general population-based study where the respondents come from different working environment.

5.10 Conclusion

In conclusion, this study revealed a substantial portion of exposed subjects had at least one self-reported LAA symptoms (58%) and detected impaired lung function (56.3%). Majority were reporting nasal and upper respiratory symptoms however no case of occupational asthma was discovered. The development of LAA among the exposed group was statistically significant while compared to the control group. Besides that, a significant amount of the exposed workers who reported at least one LAA symptoms also recorded decline lung function (37.9%). However, one-fifth (18.4%) were found to be asymptomatic somehow detected abnormal lung profile in the spirometry test. The exposed group evidently showed significantly worse lung values compared to the control subjects. For the associated risk factors, being male, those not fully compliance to PPE usage at all time, workers with underlying atopy and the positive smoking status were found more likely to develop LAA. The present study indicated that individualized occupational preventive program for risky workers in contact with experimental animals is imperative and mandatory. Exposure avoidance or reduction with appropriate health monitoring must be implemented for all Individuals with positive LAA .LAA has excellent prognosis when the exposure can be avoided, while reducing the exposure could be the primary control .The constant active clinical survey can be an effective measure to track the development of allergies spectrum in both individuals and exposed group, besides improving occupational health management as well as to prevent the progression into chronic disability. The medical surveillance program is the effective measures to track the development of LAA

among the exposed individuals therefore it is useful in improving health management besides preventing the disease progression.



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LABORATORY ANIMAL ALLERGY QUESTIONNAIRE
FOR LABORATORY ANIMAL WORKERS

PART A- Socio-demographic Information

- 1.Name: _____
- 2.Age: _____
- 3.Gender: male / female
- 4.Race: Malay/ Chinese/ Indian/ others
- 5.Educational background: primary/ secondary/ tertiary
- 6.Address: _____

PART B- EMPLOYMENT HISTORY

- 1.Job Title: _____
- 2.How many years/ months in current position: _____
- 3.Number of years employed at this facility: _____
- 4.Prior to employment at this facility, did you work with laboratory animal?
☐ Yes ☐ No
If yes, _____ year/s
Type of animals: _____

PART C- PRESENT JOB

In the past 12 months, please tick the appropriate :

1. Does your work involve contacting or handling animals?
☐ Yes ☐ No
2. Does your work involve contacting or handling animals' excreta, contaminated plant or equipment?
☐ Yes ☐ No
3. Does you work in an environment with animals or their dander?
☐ Yes ☐ No
4. Work area: ☐ Animal house ☐ Laboratory

PART D- OCCUPATIONAL HISTORY / HISTORY OF CONTACT AND EXPOSURE

1. Describe the duties especially nature of work with animals, their excreta or environment:
(please tick at the relevant duties)

Handling stool or urine	<input type="checkbox"/>
Collect blood / Harvest tissue	<input type="checkbox"/>
Dissection/ surgical procedure	<input type="checkbox"/>
Handling soiled bedding	<input type="checkbox"/>
Feeding/ breeding	<input type="checkbox"/>
Change bedding/ cleaning of cages	<input type="checkbox"/>
Handling carcasses	<input type="checkbox"/>
Vaccination/ injection	<input type="checkbox"/>

Others: _____

2. Have you worked with laboratory animals or their excreta in recent 12 months?
If yes, complete the following:

Type of Animal	Duration and frequency of contact					
	Duration in Years	Daily	Hours per day	At least one a week	Hours per week	Less than once a week
Mouse		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Rat		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Hamster		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Guinea pig		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Rabbit		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Goat		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Monkey		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Cat		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
Others:		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>

3. Do you use or wear the following items when working with animals at this facility at all the time?

Personal Protective Equipment	Use all the time		Easily accessible	
	Yes	No	Yes	No
Protective eye glasses	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Surgical mask	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Respirator	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lab gown / apron	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gloves	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Safety shoes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

PART E- PRESENT SYMPTOMS

1. Do you regularly or frequently have the following symptoms upon animals contact?

Symptoms	No	Yes	Year of onset	At work	At home	On vacation	No difference
Watery/ Itchy eyes	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swollen eyes or lips	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Skin rashes/itchiness	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stuffy/ congested nose	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequent runny nose	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequent sneezing	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequent cough	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wheezing	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shortness of breath	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chest tightness	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Asthmatic attack	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. How soon after exposure to laboratory animals do these symptoms started?

Less than 10 minutes ☐ 10 minutes- 1 hour

1 to 8 hours ☐ more than 8 hours

3. How long do these symptoms last ?

☐ Less than 10 minutes ☐ 10 minutes- 1 hour

☐ 1 to 8 hours ☐ more than 8 hours

PART F- HOME ENVIRONMENT/ PAST HEALTH INFORMATION

1. Do you have indoor pets? ☐ Yes ☐ No
If yes, what type of animals: _____
For how long in years/ months: _____
2. Do you smoke? ☐ Yes ☐ No
If yes, how many cigarettes per day? _____
For how many years? _____
Have you ever been a smoker? ☐ Yes ☐ No
If yes, when did you stop smoking? _____
At what age did you start smoking? _____
How many cigarettes per day? _____
3. Were you told by doctor that you had allergies to animals? ☐ Yes ☐ No
If yes, what type of animal? _____
4. Have you ever received treatment for allergic reaction? ☐ Yes ☐ No
5. Has a doctor ever diagnosed you for having asthma? ☐ Yes ☐ No
If yes, at what age did your asthma start? _____
When was your last asthmatic attack? _____
Are you currently taking any medication to control your asthma? ☐ Yes ☐ No
6. Do any of your blood of kin (grandparents, parents and brothers / sisters) have allergies
Or asthma? ☐ Yes ☐ No
7. Are you under medical care for any chronic illness? ☐ Yes ☐ No
If yes, please specify: _____
8. Are you on any regular medicine? ☐ Yes ☐ No
If yes, please specify: _____

-----THE END OF QUESTIONNAIRE-----

THANK YOU



CONSENT FORM

Title of research :

LABORATORY ANIMAL ALLERGY (LAA) AMONG THE ANIMAL FACILITIES' WORKERS IN A RESEARCH INSTITUTE: A CLINICAL SURVEY

To become a participant in this research, you are advised to sign this consent form.

I herewith confirm that I have met the requirement of age and am capable of acting on behalf of myself as follows:

1. I understand the nature and scope of the research being undertaken.
2. All my questions relating to this research and my participation therein have been answered to my satisfaction.
3. I voluntarily agree to take part in this research, to follow the study procedures and to provide all necessary information to the investigators as requested.
4. I may at any time choose to withdraw from this research.
5. Except for damage resulting from negligent or malicious conduct of the researcher, I hereby release and discharge Universiti Utara Malaysia and all participating researchers from all liability associated with, arising out of, or related to my participation and agree to hold them harmless from any harm or loss that may be incurred by me due to my participation in this research.
6. I have read and understood all the terms and conditions of my participation in the research.

I have read the statements above, understand the same, and voluntarily sign this form.

Name of participant :

IC/ Passport number:

Phone number :

Signature:

Date :



BORANG KEBENARAN

Tajuk Penyelidikan :

LABORATORY ANIMAL ALLERGY (LAA) AMONG THE ANIMAL FACILITIES' WORKERS IN A RESEARCH INSTITUTE: A CLINICAL SURVEY

Untuk menjadi peserta dalam penyelidikan ini, anda dinasihati untuk menandatangani borang kebenaran ini.

Dengan menandatangani mukasurat ini, saya mengesahkan yang berikut:

1. Saya memahami skop penyelidikan yang dijalankan.
2. Saya berpuas hati dengan semua soalan dan penglibatan saya dalam penyelidikan ini
3. Saya secara sukarela mengambil bahagian dalam penyelidikan ini, mengikut segala prosedur dan memberikan maklumat yang bersesuaian seperti yang diminta oleh penyelidik.
4. Saya boleh memilih untuk menarik diri daripada penyelidikan ini.
5. Kecuali bagi kerosakan yang berlaku akibat daripada perlakuan cuai atau niat jahat penyelidik, saya dengan ini melepaskan penyelidik dari Universiti Utara Malaysia daripada segala tanggungjawab yang dikaitkan, yang timbul atau berkaitan dengan penyertaan saya. Saya juga bersetuju untuk melepaskan penyelidik daripada sebarang bahaya atau kerugian yang mungkin disebabkan oleh saya melalui penyelidikan ini.
6. Saya telah membaca dan memahami semua terma dan syarat berkenaan penglibatan saya dalam penyelidikan ini.

Saya telah membaca pernyataan di atas, memahami, dan secara sukarela menandatangani borang ini

Nama peserta :
No kad pengenalan :
No telefon :
Tandatangan:
Tarikh :